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EFFICACY OF ANTIMICROBIAL AND ANTIFUNGAL AGENTS

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RECENT SYMPOSIA

November, 1969
BASES OF THERAPY

January, 1970
MODERN CHALLENGES IN MEDICINE

March, 1970
DIFFICULT MEDICAL PROBLEMS

May, 1970
NEW DEVELOPMENTS IN MEDICINE

July, 1970
SOPHISTICATED DIAGNOSTIC PROCEDURES

FORTHCOMING SYMPOSIA

November, 1970
CURRENT CONCEPTS IN CLINICAL NUTRITION
SEYMOUR LIONEL HALPERN, M.D., *Guest Editor*

January, 1971
DISEASES OF THE KIDNEY
ROBERT M. KARK, F.R.C.P.,
FRANKLIN D. SCHWARTZ, M.D., *Guest Editors*

March, 1971
TREATMENT OF COMMON MEDICAL DISORDERS
JOSE S. BOCLES, M.D., *Guest Editor*

May, 1971
MEDICAL ADVANCES IN CANCER
IRWIN H. KRAKOFF, M.D., *Guest Editor*

July, 1971
DIABETES MELLITUS
PHILIP FELIG, M.D.,
PHILIP K. BONDY, M.D., *Guest Editors*

Table of Contents

SYMPOSIUM ON EFFICACY OF ANTIMICROBIAL AND ANTIFUNGAL AGENTS

SYMPOSIUM ON EFFICACY OF ANTIBIOTIC AND ANTIFUNGAL AGENTS

Foreword

In the late nineteen thirties, it was my good fortune as a medical student to be present when Dr. Perrin Long gave a report of the treatment of pneumonia with one of the first sulfonamides. His findings were greeted with much skepticism and little enthusiasm. Some who were present expressed the opinion that the good results came about more from the selection of patients who would be expected to do well than from any therapeutic effectiveness of the drug itself. High hopes had been held before for many new drugs that had not lived up to their early promises.

HOWARD F. CONN, M.D.

None of us had an inkling of what was to come with the antibiotic age. The advent of penicillin soon sparked the search for other antibiotic compounds. At first it appeared that these would prove to be ideal agents, but reports of toxicity, side effects, unexplained failures, and undesirable complications soon dispelled this hope. We now know that antibiotics, like any other therapeutic agent, are subject in spite of their great value to definite limitations.

In the 33 years since Dr. Long gave his report a vast amount of research in the use of antibiotic agents has taken place and it seems appropriate at this time to present a symposium on the efficacy and proper use of these agents. It is hoped the information given here will be of help to the physician in making the difficult decisions so often posed in the selection of proper antibiotic therapy.

Most of the older and more familiar agents are dealt with in this symposium, though in many instances newly emerging patterns of clinical usefulness make an updated review a timely necessity for the practicing physician. In addition, gentamicin and cephalexin – brand-new antibiotics – are given a place here, and their potential future is assessed.

Thanks are due to all of the expert contributors, who have given generously of their time to share with others the knowledge and experience so carefully collected.

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The Use of Sulfonamides in
Urinary Tract Infection

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Overall indications for the use of sulfonamides are few. They are used for prophylaxis against group A streptococcal infections in patients with rheumatic cardiovascular disease who are sensitive to penicillin. Combinations of sulfonamides and other antimicrobials are effective against Nocardia infections, trachoma, toxoplasmosis, pneumocystis carinii infections, and some other infrequent or minor infections. Their greatest use is in the treatment of uncomplicated, nonrecurrent, acute urinary tract infections caused by a variety of microorganisms. Their low cost, ease of administration, safety, and high order of efficacy against a broad spectrum of urinary pathogens are special recommendations for this class of drugs.

The sulfonamides represent drugs of first choice in the treatment of initial acute uncomplicated urinary tract infection. Whether or not bactericidal agents (such as ampicillin) may be more useful than the bacteriostatic sulfonamides is not known. It is difficult enough to determine which member of the sulfonamide group of drugs is the most effective, and the literature is controversial and replete with conflicting claims. Suffice it to state that sulfadiazine, sulfamerazine, and sulfamethazine, alone or as mixtures of two or more, and sulfisoxazole have all been used with effectiveness. The use of the newer derivatives of sulfonamides presently available under various trade names is not recommended on the ground that they do not have a long and clearly proved history of clinical use and effectiveness.

As experience and confidence in the less toxic sulfas have grown, their use is no longer accompanied by meticulous and frequent examinations of urine and blood to detect hematuria, cylindruria, or anemia. Nonetheless, it is important that care be exercised in their administration, and that their use not be indiscriminate or lacking in close surveillance by the physician.

In any contemplation of the use of sulfonamides in the treatment of urinary tract infection, due consideration must be given to the fact

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that the most serious and frequent complications from the systemic administration of sulfonamides are related to the urinary tract.[1] Urinary tract complications caused by sulfonamides are of three major types: (1) crystalluria (most common type), (2) toxic nephrosis (less common, more serious), and (3) hypersensitivity reactions (rare, often serious, may be fatal). Nissen and his associates[3] have carefully examined the frequency of injury to the urinary tract by various commonly used sulfonamides and have found it to be approximately the same (gross or microscopic hematuria in less than 2 per cent of cases).

We use a mixture of sulfonamides[*] in our clinic[4] for the following reasons: (1) chemical and clinical studies of sulfadiazine, sulfamerazine, and sulfamethazine in combination have demonstrated that the total amount of sulfonamide that can be held in solution in urine is substantially increased when two or more of these substances are administered simultaneously; (2) this is accomplished without sacrificing therapeutic activity; (3) it has also been demonstrated that such a mixture is more soluble at pH 5.5 and below than any single soluble sulfonamide. Finally, it may be pointed out that milligram for milligram the sulfonamides contained in the mixture are more active than the dimethyl sulfonamides such as sulfisoxazole or sulfadimetine.

Nonetheless, in view of the lack of data pointing to an unmistakable clinical superiority of the mixture or sulfisoxazole, it would seem wise for the clinician to choose one or the other in his management of renal infections and to learn to use it well.

In our own experience gross hematuria has not been encountered, although microscopic hematuria is occasionally observed. Sulfonamides have had to be discontinued in about 2 per cent of our child patients; in one group of children treated during a particularly hot and prolonged summer, skin rashes occurred in about 6 per cent. It was at this time that we became acutely aware of the element of heliosensitivity in the rashes of certain patients, and undue exposure to sunlight was interdicted. Because there is some evidence that the incidence of drug rash and fever increases in direct proportion to the dose of sulfonamide, we have also decreased the amount administered during the height of summer.

The use of these agents has been gratifyingly free of toxicity in our hands, but we are exquisitely sensitive to their potential for producing serious and even fatal consequences. Warning signals, most commonly hematuria and skin rash, but also chills, fever, weakness, vomiting, jaundice, headache, and sore throat, must not be ignored. It is useful to know that acute hemolytic anemia, if it is to occur, will most likely do so during the first week of administration, and that leukopenia or agranulocytosis tends to occur during the third or fourth week of therapy.[1] Absolute contraindications to the use of sulfonamides are few. The main one is hypersensitivity to the drug as indicated by a previous toxic reaction to it, such as a severe dermatitis, acute hemolytic anemia, purpura, fever, or jaundice.

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[*] Trisulfapyrimidines USP (Sulfose, Wyeth)

The long-acting sulfonamides, sulfadimethoxine (Madribon) and sulfamethoxypyridazine (Kynex, Midicel), are not recommended for either therapy or prophylaxis because of serious toxic reactions which have been disturbing in their number; several deaths from hypersensitivity have been reported.[5]

It is our practice to use the mixture of sulfadiazine, sulfamerazine, and sulfamethazine in all initial acute infections of the kidney and urinary tract and in a dosage of 100 to 150 mg. per kg. of body weight per day in 3 or 4 divided doses by mouth; the dosage is the same for sulfisoxazole.* In vitro sensitivity tests with sulfonamides, as usually performed, are unreliable; in vivo results often do not agree with such sensitivity tests. This is probably related to the fact that while blood levels of sulfonamide easily attainable following the usual therapeutic doses may reach 50 micrograms per ml. (5 mg. per 100 ml.), urine levels may be 10 times higher.[2] Under these circumstances it is felt that the best sensitivity test is the patient himself; we will culture a clean-voided sample of the patient's urine 24 to 48 hours after administration of the drug to make sure the bacteria have been eliminated. If they have not been eliminated, a comprehensive urologic examination is required. One should not change to another drug without carrying out such an examination with an appropriate consultant in urology. Rarely will failure to eradicate a first infection be due to resistance of the organism to the chemotherapeutic agent. Rather, it will be due to some impairment of urine flow secondary to a structural or functional abnormality, or both, in the urinary system.

If the bacteria have been eliminated, treatment is continued for 10 days to 2 weeks, after which time the patient is followed at monthly intervals for 3 months, and then every 3 months thereafter. At each visit, a careful interim history should be obtained, physical examination should be carried out as required, and urinalysis and a quantitative urine culture should be obtained. If the patient has no further infections after a year of follow-up, he should be seen at 6 month intervals for another year, and then discharged. Examination of the urine should always be carried out thereafter whenever a febrile illness occurs — *regardless of symptoms.*

Most of the recurrences of infection, if they are to occur, will take place within 18 to 24 months following the initial infection, and this is the period during which careful follow-up is essential. The operative word here is *follow-up*. With diligent follow-up assured, one may wait until infection recurs before seeking urographic examination. In dealing with a clinic population, we obtain an intravenous pyelogram during the second week of treatment of the initial acute infection, or shortly thereafter, in order to provide an opportunity for the inflammatory changes to subside. In this way, erroneous over-interpretation of the disease processes may be avoided.

Bacteriologic control can be effected by use of the sulfonamides in the great majority of infections caused by the coliform organisms

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*Sulfisoxazole USP (Gantrisin, Roche)

(Escherichia coli, Paracolobactrum) and some gram-positive bacteria (staphylococci and streptococci, other than enterococci). Proteus species, Aerobacter aerogenes, and Pseudomonas are usually resistant, but on occasion can be controlled by the sulfonamides. In general, these latter microorganisms are encountered in chronic, recurrent, usually complicated (i.e., with some functional or structural defect) infections, and one is guided in these circumstances by the results of in vitro susceptibility tests. Since strains resistant to the sulfonamides are more likely to be encountered in such recurrent infections, the use of these drugs will not be as satisfactory as in initial acute infections.

The use of sulfonamides in long-term maintenance therapy for the suppression of bacteriuria in children with chronic infections is sometimes undertaken in children who, in the absence of a correctable structural or functional defect, nonetheless continue to have recurrent infections. The dose is reduced to one-half or one-third the recommended dosage, and the frequency of administration may often be reduced to twice daily or to a single dose given at bedtime. By careful trial and error, titrating the dose against the patient's requirements, one may arrive at the minimal effective dose for "long-term" (months to years) prophylactic maintenance therapy.

The sulfonamides are effective when used in this way, but the emergence of resistant variants of the pathogens in chronic recurrent disease diminishes their utility.

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The Natural Penicillins

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During the past 15 years, vast research and development programs aimed at improving the efficacy of penicillins have come to fruition. The penicillin molecule has provided an outstanding example of extremely broad biological activity as well as the value of molecular manipulation in achieving additional therapeutic efficacy. The acid stability of penicillin has been increased; the antibacterial spectrum has been extended to include even Pseudomonas, and other forms resistant to degradation by β-lactamase have been produced. Despite these successes, the natural penicillins, benzylpenicillin G and phenoxymethyl penicillin, remain the drugs of choice in treating infections due to susceptible organisms because of their proven effectiveness, low cost, ease of administration, readily manipulated dosage schedules, and relatively low incidence of side effects. This paper reviews the pharmacology, indications, and reactions related to these valuable antibiotics.

By definition the natural penicillins are those produced biosynthetically. A high yielding ultraviolet mutant strain of Penicillium chrysogenum is added to 20,000 gallon tank fermenters. After days of carefully controlled agitation and fermentation, a final concentration of penicillin in the crude culture medium should be 15,000 to 18,000 units per ml., not far from a daily dose shown to be effective for pneumococcal pneumonia in the early 1940's. The principal yield of this process is benzylpenicillin G. Early studies showed that the addition of precursors to the fermentation medium resulted in penicillins whose antibacterial and intrinsic properties differed from those of penicillin G. Penicillins F, K, N, X, O, and V were investigated extensively. With the exception of penicillin V, the others remain of historical interest only. The addition of phenylacetic acid to the culture medium ensures a high yield of penicillin G, whereas addition of phenoxyacetic acid results in the fungus producing phenoxymethyl penicillin (penicillin V).

The structure of penicillin is shown in Figure 1. Condensation of

Figure 1. Synthesis of natural penicillins. *A*, Thiazolide ring; *B*, beta-lactam ring; *C*, site of beta-lactamase (penicillinase) action; *D*, site of acylation.

1-valine and 1-cysteine results in a simple dipeptide, 6 amino penicillanic acid (6 APA), containing a β-lactam ring and a thiazolidine ring. This compound is the nucleus for all the penicillins, natural and semisynthetic, explaining perhaps the cross allergenicity exhibited by all penicillins. Synthesis is completed by the acylation of a side chain, a benzyl radical in penicillin G, or a phenoxymethyl radical in penicillin V.

Enzymatic hydrolysis (deacylation) of penicillin G yields the 6 APA nucleus. The enzyme responsible for this degradation is produced by many gram-negative enteric organisms and fungi. 6 APA had been synthesized in the laboratory,[1] but the yield from a completely synthetic procedure is small. It has been practically and economically more feasible to obtain 6 APA by deacylating penicillin G, large amounts of which are available owing to highly efficient fermentation methods. The discovery that 6 APA could be obtained in this manner cleared the way for production of the semisynthetic penicillins, whose side chains confer the various differences in microbiological, pharmacological, and therapeutic activity.

The site of action of β-lactamase (penicillinase) is also shown in Figure 1. Once the β-lactam ring has been opened, 6 amino penicilloic acid is formed. This latter compound, though biologically inert, may have some chemical role in penicillin allergy.

PHARMACOLOGY

Penicillin G is unstable in sol .tion at low pH. Its half-life at pH 4.5 is approximately 24 hours, compared with a half-life of approximately 20 minutes at a pH of 1. The acid component of gastric juice rapidly inactivates orally administered penicillin G, but the remaining active drug is absorbed in the duodenum. At best, determined by the amount recovered in the urine, 15 per cent of an administered dose is absorbed. Therefore, an oral dose that is 5 times the parenteral dose should be given to achieve comparable blood levels. Maximum absorption and highest peak blood levels are achieved if the drug is taken on an empty stomach, half an hour before or 2 to 3 hours after meals. When taken as described, 400,000 units (250 mg.) will give a peak blood level at 1 hour of approximately 0.6 micrograms per ml. Six hours later, 0.1 microgram per ml. is still present (Fig. 2).

The highly soluble sodium and potassium salts of penicillin G appear rapidly in the blood after intramuscular injection, and peak blood levels depend on the dose administered. Thus, an intramuscular injection of 600,000 units, about the maximum dose which should be given by this route, results in a serum concentration of 6 to 8 micrograms per ml. at 30 minutes. Because of rapid excretion of the drug, little if any penicillin remains in the serum 4 to 6 hours later. For this reason parenteral penicillin G is conventionally administered every 4 to 6 hours.

The salt and vehicle, by altering the solubility of penicillin, may result in delayed absorption. Procaine salts of penicillin G consist of equimolar amounts of procaine and penicillin. Solubility is relatively low (4.4 mg. per ml.), and the injected material dissolves slowly. Moderate serum levels are obtained and can be maintained for 12 to 24
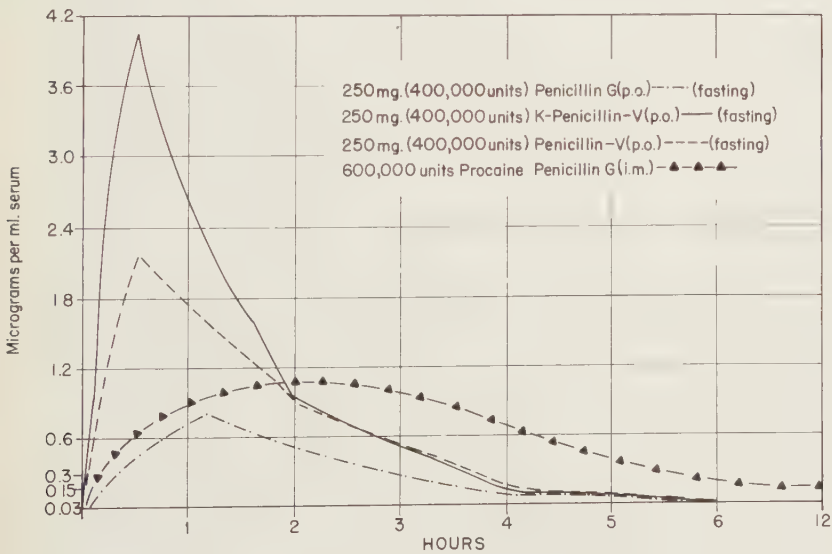

Figure 2.   Blood levels following different preparations of penicillin.

hours depending on the dose. Levels approximate 1 microgram per ml. 2 hours after an intramuscular dose of 600,000 units, and detectable levels (0.06 microgram per ml.) are present for 12 hours (Fig. 2). Raising the dose above 600,000 units does little towards increasing peak levels, but prolongs the time during which penicillin can be detected in the serum. In treating most infections for which procaine penicillin G is suitable therapy, the dose is repeated at 12-hour intervals.

The benzathine salt of penicillin G is minimally (0.135 mg. per ml.) soluble in water. Low blood levels are achieved but are maintained for long periods of time. After 600,000 units are injected intramuscularly, 0.02 micrograms per ml. are detectable for 12 days. The duration of demonstrable serum levels may be lengthened to 4 weeks by administration of 1.2 million units. Benzathine penicillin G is also available in tablet form for oral administration. Although its clinical efficacy in rheumatic fever prophylaxis has been established, absorption is irregular and unpredictable, and other more reliable preparations are preferable for oral use.

Phenoxymethyl penicillin is not inactivated by the acidity of gastric juice, and is readily absorbed in the neutral or alkaline environs of the duodenum. Peak serum concentrations occur earlier and are higher in the fasting state, but total absorption is not influenced by the timing of the dose in relation to meals. The potassium salt provides higher peak levels in the fasting state because it is better absorbed. Serum levels exceed those achieved with oral penicillin G by three to four times. Absorption is nonetheless far from complete, and only 35 to 40 per cent is recoverable in the urine. Peak blood levels 30 minutes after 400,000 units (250 mg.) are 1.5 to 2 micrograms per ml., and after 800,000 units (500 mg.), 3 to 4 micrograms per ml. Four hours later only 0.3 microgram per ml. is still present, and little or no drug is detectable 6 hours after administration (Fig. 2). The daily dose of penicillin V may be as low as 1000 mg. for minor infections or as high as 6000 mg. for infections such as endocarditis.

EXCRETION

Penicillins are excreted primarily by the kidney. Glomerular filtration (10 per cent) and active proximal tubular secretion (90 per cent) account for the rapid clearance. After parenteral administration of potassium penicillin G, 75 to 90 per cent of a given dose is recoverable in the urine, 50 to 60 per cent of the drug being recovered within the first hour. By blocking tubular secretion of penicillin and competing with it for binding sites on serum albumin, probenecid decreases the rate of excretion and increases penicillin serum levels two to three times. As renal function deteriorates, the serum half-life of penicillin increases,[31] and higher tissue levels result. If large doses are administered to patients with impaired renal function, cumulative serum levels of several hundred micrograms per ml. may be reached. This in turn leads to elevated cerebrospinal fluid levels and signs of neurotoxicity.

Sustained serum levels may occur in premature infants and neonates less than 3 days of age.[1] As tubular function matures, penicillin is cleared more rapidly, and infants above 3 months of age handle penicillin similarly to adults. The normal deterioration of renal function with age suggests that doses over 40 million units per day not be given to patients over 50 years of age unless the indication is strong and blood levels can be monitored.[21]

Normally a small but undetermined amount of penicillin is removed by biliary excretion. After bilateral nephrectomy in dogs, a major portion of penicillin is eliminated in the bile.[2] That this mechanism plays a role in man is evidenced by the fact that the half-life of penicillin in anuric patients with hepatic failure is 2 to 3 times longer than in anuric patients with normal liver function.[20]

The penicillins are excreted unchanged, metabolic products rarely being recovered in vivo. 6 APA was found in the urine of one patient receiving oral penicillin G.[7] It was theorized that enzymes of enteric bacteria had de-acylated penicillin G, and 6 APA was absorbed and excreted. In the presence of renal failure penicillin may be inactivated by hepatic acylases.[17]

Penicillin is loosely bound to serum albumin to a degree which varies with both the method of study and the reporting investigator. Approximately 50 per cent of the total drug in serum is loosely bound, and as unbound drug is excreted, the protein-penicillin complex dissociates, liberating more free penicillin until a new equilibrium is reached. Binding to tissue proteins does not occur. In the case of the natural penicillins, protein-binding does not interfere with therapeutic efficiency.[19] Therapeutic levels are easily achieved under normal circumstances in extracellular fluid and most other body tissue, except bone and muscle. Penicillin crosses the placenta, and although levels are higher in maternal blood, it appears in the fetal circulation 60 to 90 minutes after administration to the mother.[17] Penetration into avascular areas, abscesses, or fibrin matrices may be reduced, necessitating large amounts of penicillin in the treatment of some infectious processes.

Under normal circumstances, only low concentrations of penicillin have been demonstrated in cerebrospinal fluid even after large doses. Penicillin may, however, enter the spinal fluid but be actively transported back into the blood by a secretory mechanism similar to that which exists in the renal tubule. Probenecid appears to inhibit this transport, thereby increasing cerebrospinal fluid levels.[10, 11] In the presence of inflammation, penetration across all serous membranes is enhanced, and therapeutic levels are reached in joint spaces, body cavities, and spinal fluid, owing perhaps, at least in the latter instance, to interference with active transport out of the cerebrospinal fluid.

CLINICAL INDICATIONS

The indications for use of the natural penicillins are infections due to susceptible organisms. Generalizations can be made concerning

the preparation, the dosage, and the duration of therapy, based on knowledge of the usual range of sensitivity of organisms to penicillin, achievable serum and body fluid levels of penicillin, and clinical experience. The final decision should be based on the nature of the infecting organism, the type and extent of the infection, and the general condition of the patient. Results of in vitro sensitivity tests may influence the plan for chemotherapy, and in some instances tube dilution sensitivities may be helpful.

Achieving a blood level that is five times the concentration of penicillin inhibiting the growth of the organism in vitro (the MIC) has often been recommended. The doses used in practice usually result in blood levels that are far in excess of this goal. Early experience suggests that many infections could be cured satisfactorily using smaller doses than are currently employed. On the other hand, the potential sequelae of undertreating are more serious than the adverse effects associated with current conventional therapy.

The controversy over continuous versus intermittent antibiotic therapy remains unsettled. The vagaries and uncertainties of continuous therapy as generally practiced are substantial. Further reference to daily doses of parenteral penicillin implies intermittent administration, generally at 4-hour intervals, for the average adult with normal renal function and no history of penicillin allergy. Modification may be necessary when treating children, and some reduction in dosage may be appropriate if large doses are administered to patients with compromised renal function.

It should be re-emphasized that precise information regarding dosage, even after 25 years of clinical experience, is not well defined, possibly because of the wide dosage range which is possible with the natural penicillins. It appears reasonable that an individual patient may require more or less penicillin, depending on the extent of his infection and his ability to respond to that infection. Furthermore, these recommendations assume correct identification of the infecting organism. Treatment of infectious processes before the etiology has been determined is empirical and often may not include a natural penicillin. One of the semisynthetic penicillins such as ampicillin or a penicillinase-resistant penicillin may be the agent of choice for initiating treatment, as in purulent meningitis of uncertain type or suspected staphylococcal sepsis. After a clear bacteriological diagnosis is made, a switch to penicillin G or V may be justified to minimize cost, side effects, or both.

SPECIFIC INFECTIONS

Pharyngitis

Group A beta-hemolytic streptococci are responsible for nearly all instances of bacterial pharyngitis and tonsillitis, although bacterial causes are responsible for less than half the cases of "sore throat." All these organisms remain sensitive to minute amounts of penicillin. Oral therapy with 250 mg. of penicillin V every 6 to 8 hours for 10 days

is adequate for these cases. Relapse or recurrence rates of 7 to 18 per cent are probably due primarily to failure of the patient to complete the full duration of therapy.[12, 16] A single injection of benzathine penicillin 1.2 million units is an alternative mode of therapy. Microaerophilic and anaerobic streptococci, Bacteroides species and fusobacteria are frequently involved in a variety of infectious processes in and about the mouth. Conditions such as Vincent's or Ludwig's angina, facial cellulitis, and abscesses may develop in association with poor oral hygiene or following dental extractions. Especially if these patients manifest systemic signs of infection, parenteral penicillin G, 4 to 6 million units per day is preferable as initial therapy until the acute manifestations of infection subside, when oral penicillin V can be substituted to complete a 7 to 10 day course of therapy.

In pharyngeal and related forms of Corynebacterium diphtheriae infections, antibiotics are but a part of the total therapy and probably do not influence the clinical course. Procaine penicillin, 1.2 million units per day, will eradicate sensitive organisms, though a small percentage of recovered patients remain carriers. The carriage of both C. diphtheria and group A beta-hemolytic streptococci should be treated and is often eliminated by a 10 day course of oral penicillin V.

Otitis Media

Hemophilus influenzae is commonly responsible for acute bacterial otitis media in children below the age of 6. In this age group, therefore, penicillin V plus a sulfonamide, or ampicillin alone, is preferred therapy.[29] In older children and adults pneumococci and group A hemolytic streptococci are almost exclusively the causative organisms. Penicillin V, 250 mg. every 6 hours for 7 days, is recommended. The role of penicillin-resistant Staphylococcus aureus, gram-negative bacilli, especially Proteus and Pseudomonas species, and possibly anaerobic cocci and bacilli, is more important in chronic otitis media. Appropriate therapy will depend on the infecting organisms as well as the local anatomical abnormalities responsible for persistent or recurrent infection.

Acute bacterial sinusitis is presumably caused primarily by gram-positive cocci. Pneumococci and streptococci are the most commonly isolated organisms, but good bacteriological studies of these infections are relatively few. Staphylococcal infection and mixed infections with aerobic and anaerobic organisms of the oropharynx may occur. For minor infections penicillin may be administered as for otitis media. For acutely ill, toxic patients, especially those in whom the possibility of intracranial extension exists, 10 to 15 million units of penicillin G should be given intravenously in divided doses.

Cellulitis

Beta-hemolytic streptococcal cellulitis and lymphangitis (erysipelas) respond well to penicillin. Minor infections require modest amounts of procaine penicillin or penicillin V. Higher doses of aqueous penicillin should be given for extensive infections, or if patients have systemic illness. Mixed aerobic and anaerobic cellulitis may occur seemingly spontaneously, or after surgical procedures or trauma. Large doses of

penicillin G administered intravenously, for example, 20 million units per day, are recommended. These synergistic infections require debridement, and additional antibiotics effective against gram-negative organisms or penicillinase-producing staphylococci may be indicated by the bacteriology of individual cases. Similar recommendations obtain for clostridial cellulitis and gas gangrene.

Pneumonia

If nosocomial infections are excluded, the pneumococcus remains the predominant cause of pneumonia, and all pneumococci are exquisitely sensitive to penicillin. If the pneumonia is confined to a single lobe and the patient is not seriously ill, either 600,000 units of procaine penicillin every 12 hours or 250 to 500 mg. penicillin V every 6 hours will provide satisfactory treatment. Patients in the older age groups, those with multiple lobe involvement or serious underlying disease, or those with systemic manifestations suggesting the possibility of bacteremia, are more appropriately treated with 6 to 10 million units of potassium penicillin G parenterally. Therapy should be continued for at least 5 days after the patient is afebrile.

Pneumonia due to coagulase-positive Staphylococcus aureus should be treated with penicillin G if adequate in vitro sensitivity tests (Kirby-Bauer disc technique or tube dilution method) have established that the organism does not produce penicillinase. If it is sensitive to 0.2 micrograms per ml. or less of penicillin, it is a non-penicillinase producer and penicillin G will be 10 to 20 times more active than the penicillinase-resistant semisynthetic penicillins. Treatment under these circumstances should be 6 to 10 million units of penicillin per day until the infection is well controlled, after which oral penicillin V may be substituted to complete a total of 4 to 6 weeks of treatment.

Beta-hemolytic streptococcal pneumonia occurs infrequently in adults. Most cases follow viral pneumonia, and particularly varicella, influenza, and rubeola, and are most troublesome when complicated by early empyema. Penicillin G should be given in a daily dose of 10 to 12 million units for 3 to 4 weeks.

Aspiration pneumonia and lung abscess are caused, either wholly or in part, by aerobic, microaerophilic, and anaerobic microorganisms originating in the mouth. Adequate bronchial drainage is of paramount importance, and penicillin G is the antibiotic of choice. In some circumstances a second drug may be indicated, based upon sputum cultures at various stages of the disease. Potassium penicillin G, 10 to 20 million units intravenously per day, should be administered initially. Further dosage and duration of therapy will depend on the evolution of the pulmonary process. Five days of therapy may be sufficient in uncomplicated aspiration (probably at dosage levels appreciably less than for an established lung abscess), whereas several months of therapy may be indicated in treating cavitary pneumonia, abscess, or empyema.

Meningitis

Pneumococcal and meningococcal meningitis are the most common pyogenic meningitides in adults. The preponderance of group B sulfa-

resistant strains of meningococci in meningitis has made penicillin G the agent of choice in managing gram-positive meningitis. An initial intravenous dose of 5 million units is followed by 2 million units every 2 hours. It is unnecessary to administer intrathecal penicillin in these diseases. Hemophilus influenza meningitis occurs rarely in adults and should be treated with ampicillin. Penicillin is not effective in eliminating the meningococcal carrier state.

Endocarditis

The majority of cases of bacterial endocarditis are caused by Streptococcus viridans, which is almost always quite sensitive to penicillin. Resistant organisms may become predominant in the oral cavity and upper respiratory tract when sensitive strains have been eradicated by prior penicillin therapy, especially after oral prophylaxis of rheumatic fever. Several alternative therapeutic regimens appear to be satisfactory for treatment of endocarditis due to penicillin-sensitive alpha hemolytic streptococci. Because all the regimens reported are relatively effective, large numbers of cases would be needed to evaluate small differences in cure and relapse rates on the different schedules.

Conventional therapy consist of potassium penicillin G, 3 to 5 million units per day intravenously, for 4 weeks. Oral penicillin V, 4.5 to 7 gm. per day, alone or in combination with streptomycin, has been shown to be effective.[13, 35] Even physicians who are apprehensive of oral therapy or especially concerned for the patient with aortic valve disease should probably accept a decreased duration of parenteral therapy. If in vitro sensitivity testing by a tube dilution method has revealed an organism sensitive to 0.2 micrograms per ml. or less, 2 weeks of 3 to 5 million units of penicillin G per day followed by 2 weeks of penicillin V, one gram every 6 hours, provides good therapy. Occasional cases may be due to more resistant Streptococcus viridans. They should be treated with parenteral penicillin G in dosages designed to produce blood levels at least 5 to 8 times the sensitivity of the organism. Serum bactericidal levels and penicillin levels may be performed; but if the clinical response is good, the necessity for performing these tests is questionable, and their correlation with clinical cure remains unproven.

Enterococci (group D streptococci) may be alpha-hemolytic, beta-hemolytic, or non-hemolytic, and are more resistant to penicillin than viridans streptococci. Laboratory differentiation of these streptococci is extremely important for providing effective treatment. The rate at which they are killed in vitro by penicillin is slower than for other streptococci. Aminoglycoside antibiotics, streptomycin, kanamycin, and gentamycin accelerate bactericidal activity and best exemplify true antibiotic synergism.[11] This synergism forms the basis for the use of streptomycin, 500 mg. twice daily, along with 20 million units of penicillin G per day as the initial treatment of this form of endocarditis. Larger doses of penicillin and detailed laboratory studies of the penicillin and streptomycin sensitivities of the specific organism may be helpful if clinical response does not occur. Treatment should be continued for a minimum of 4 weeks and, if possible, for 6 weeks. Discontinuance or a lowered dose of streptomycin may be necessary during treatment to prevent or minimize vestibular toxicity.

Endocarditis due to group A, B, or C beta-hemolytic streptococci is rarely encountered, and pneumococcal endocarditis, though less frequent than in the pre-antibiotic era, is still encountered occasionally. Endocarditis due to Staphylococcus aureus is considerably more frequent and coexists in about 20 per cent of staphylococcal bacteremias. Potassium penicillin G, 20 million units per day, is indicated. As in other staphylococcal infections this should only be done if the sensitivity to penicillin G is clearly established. Treatment for 4 weeks should be sufficient for pneumococcal or streptococcal endocarditis, but penicillin therapy should be maintained for a minimum of 6 weeks in staphylococcal bacteremia, with or without proven endocarditis.

Staphylococci other than coagulase-positive strains have variable penicillin sensitivity. Recent isolates at UCLA have been resistant to penicillin G as well as to the penicillinase-resistant semisynthetic penicillins. These organisms cause endocarditis in patients with congenital and rheumatic heart disease and are the most frequent cause of endocarditis following cardiac surgery.

Arthritis and Osteomyelitis

Pyogenic arthritis is seen primarily as a complication of gonococcal infection, local steroid injections for noninfectious joint disease, as an extension of osteomyelitis, or as a result of trauma or surgical procedures. Because N. gonorrheae has shown a progressive decrease in penicillin sensitivity, treatment for gonococcal arthritis consists of 5 to 10 million units of potassium penicillin G per day. After all signs of acute inflammation have abated, therapy with penicillin V (2 gm. per day) may be substituted and continued for a total course of 21 days. Staphylococcus aureus constitutes the cause for the majority of the remaining types of pyogenic arthritis and most cases of acute and chronic osteomyelitis. The guidelines for therapy are quite similar to those for pneumonia with the additional very important provision for adequate drainage of purulent exudates or removal of sequestra or foreign bodies.

Venereal Infection

GONORRHEA. Although most therapeutic studies do not include correlations of increasing in vitro penicillin resistance and clinical refractoriness, ample evidence exists that the MIC of penicillin for many strains of the gonococcus has increased. Nearly all strains are still sensitive to 1.0 microgram per ml. or less,[17] but some have been reported to require as high as 2 to 3 micrograms per ml. to inhibit growth.[37] Failure in treating gonorrhea in the male has been reported with increasing frequency in the last 5 years, presumably because of increased resistance to this antibiotic. Twenty to thirty per cent rates of relapse have been reported after administration of 2.4 million units of procaine penicillin.[15, 27] If probenecid is given prior to penicillin treatment, the resulting higher peak blood level appears to significantly decrease the failure rate. At the present time the optimal therapy of uncomplicated gonococcal urethritis in the male is not clear and, indeed, some venereal disease clinics prefer ampicillin or tetracycline.[30] Most cases, however, will be cured with one injection of 2.4 million units

of procaine penicillin with concurrent probenecid therapy.[15, 17] Cervicitis in the female should be treated in this same way on 2 successive days.

SYPHILIS. T. pallidum is highly sensitive to penicillin. Numerous schedules have been proved effective, but all aim at achieving prolonged penicillemia rather than high serum levels. Procaine penicillin, 4.8 million units over an 8-day period (600,000 units daily), or benzathine penicillin, 2.4 million units at one session, is recommended for all forms of lues with the exception of tertiary disease. For the latter, 600,000 units of procaine penicillin for 10 days, or 2.4 million units of benzathine penicillin weekly for 4 weeks is recommended.[15]

Miscellaneous Infections

Beta-hemolytic streptococci other than groups A or D have been incriminated in a wide variety of serious infections. Bacteremia due to these organisms has recently been reviewed in detail,[6] and they are encountered in urinary tract infections, pulmonary infections, arthritis, meningitis, and endocarditis. Diabetics may be particularly susceptible and infections may follow urological surgery. These organisms are slightly less sensitive to penicillin in vitro, but penicillin G is the drug of choice, in essentially the same doses recommended for infections caused by group A streptococci. Other infections in which penicillin G remains the drug of choice include actinomycosis and anthrax. Many gram-negative bacilli are sensitive to relatively high concentrations of penicillin G.[18] Eighty per cent of strains of E. coli, and nearly 100 per cent of strains of P. mirabilis, Salmonella, and Shigella species are killed by 100 micrograms per ml. of penicillin G. Penicillin V, however, is less than 10 per cent as effective as penicillin G. These concentrations are easily attained in the urine. Following 500 mg. of oral penicillin G every 6 hours, urinary concentrations of 150 micrograms per ml. are achieved; and concentrations approaching 750 micrograms per ml. will be found in the urine after 400,000 units aqueous penicillin G intramuscularly. Excellent clinical results have been reported in treating urinary tract infections with small doses of penicillin G,[13] and the therapeutic potential of penicillin G in this setting should be studied further. Penicillin G, 15 to 20 million units per day, should be part of the therapy of septic abortion and postpartum infection in which anaerobic organisms such as Clostridia, Streptococci, and Bacteroides species usually coexist with other gram-negative bacilli.

PROPHYLAXIS

Recurrent streptococcal pharyngitis is preventable with penicillin G, 200,000 units orally twice daily. Monthly injections of benzathine penicillin G, 1.2 million units, is an acceptable alternate. Penicillin is generally employed for prevention of complications from bacteremia following dental or other surgical procedures in patients with rheumatic and other types of heart disease. It is clear that this prophylaxis does

not attempt to prevent bacteremia. Rather it is postulated that high serum levels of penicillin during and shortly after the procedure help to sterilize the blood after bacteremia, thereby preventing valvular localization of organisms and subsequent endocarditis.

The recommendation of the American Heart Association is 500 mg. of penicillin V every 6 hours on the day of surgery and the following 2 days. Aqueous penicillin G, 600,000 units, is given at the time of surgery. Alternatively, procaine penicillin G, 600,000 units, and aqueous penicillin G, 600,000 units, are given one hour before surgery. This is followed by 600,000 units of the procaine penicillin every 12 hours for 2 days. During labor and childbirth, or other obstetric-gynecologic procedures, 500 mg. of streptomycin every 12 hours for 4 doses should be added to the above penicillin prophylaxis. Similarly, the administration of penicillin plus streptomycin may prevent enterococcal endocarditis not only in patients with rheumatic valvular disease but also in any elderly patient with a significant heart murmur who undergoes urological surgery.

Parenteral penicillin therapy even with large doses of intravenous penicillin does not eradicate sensitive alpha-streptococci from the pharynx. This has been interpreted to indicate that the pharyngeal concentration of penicillin is quite low following parenteral therapy. On the other hand, long-term oral prophylaxis with penicillin eradicates sensitive alpha-streptococci and promotes the growth of resistant oral streptococci,[12] owing to intermittent direct exposure to high concentrations of penicillin. Therefore, oral prophylaxis should be stopped several days before a planned procedure, to allow repopulation with sensitive strains.

TOXICITY

Of the available antimicrobial agents, the penicillins are the least toxic. Massive doses, in excess of 100 million units of penicillin G, have been given without adverse effects.[11] Leukopenia attributed to penicillin G has rarely been seen. Nephritis due to penicillin G has also been reported, though less frequently than that due to methicillin.[3]

Irritative reactions due to penicillin are quite common, depending on the preparation, route, and concentration of drug administered. Intramuscular aqueous potassium penicillin in excess of 600,000 units should be avoided because of pain and possible tissue damage. Sterile abscesses may develop at injection sites, and sciatic nerve irritation may follow deep gluteal injection. Thrombophlebitis may develop after intravenous administration of penicillin. Penicillin is very irritating to tissues of the central nervous system, and intrathecal doses larger than 10,000 units should be avoided if they are given at all. Arachnoiditis and myelitis have followed intrathecal or cisternal injections and, in both animals and humans, seizures follow local application of penicillin to cerebral tissues. Nausea, vomiting, or diarrhea may accompany oral therapy.

The central nervous system toxicity of parenterally administered penicillin has generally been confined to those patients with decreased renal function to whom doses of penicillin G in excess of 20 million units per day have been given.[21, 36] Such patients have manifested hyperreflexia, agitated confusion, muscular irritability, and multifocal myoclonus. Generalized seizures, coma, and fatal encephalopathy may follow. Hyponatremia has been described in some of these patients. Spinal fluid concentrations over 6 to 8 micrograms per ml. have usually been associated with this syndrome, and ventricular and cisternal levels over 200 micrograms per ml. have been noted, indicating that lumbar sac and cisternal fluid concentrations may not accurately reflect one another.[10] This type of toxicity has not yet been reported with the newer penicillins. Similar toxicity due to penicillin has been seen in patients undergoing cardiopulmonary bypass.[39]

Benzylpenicillin G is available as the sodium or potassium salt. One million units contain approximately 1.5 mEq. of cation. Administration in large amounts, therefore, may expose patients to potentially toxic amounts of cation, and the usefulness of the sodium salt for patients with renal failure and hyperkalemia is obvious. The incomplete absorption of potassium penicillin V minimizes cation toxicity even if large doses are given.

Fever may develop during penicillin therapy, and eosinophilia may or may not coexist. Commonly, the fever is remittent but it may be sustained. It is unusual during the first week of therapy, but whenever it occurs, it may be confused with superinfection or relapse. The fever generally disappears rapidly when the drug is stopped.

Following penicillin therapy, bacterial and yeast superinfections are frequent. These penicillin-resistant organisms colonize those areas where sensitive strains have been eradicated by therapy, regardless of the route of penicillin administration. In one report, colonization of the respiratory tract followed parenteral penicillin in excess of 2.4 million units daily, whereas smaller doses did not alter body flora.[26] Similar changes in normal bacterial flora are commonly thought to be responsible for post-antibiotic manifestations such as stomatitis, cheilosis, vaginitis, and diarrhea.

Although direct toxicity due to penicillin is quite minor, the problem of hypersensitivity is significant. Allergic reactions occur in 5 to 10 per cent of people who receive penicillins. The route of administration and preparation are significant, more reactions occurring with topical preparations than with parenteral forms, oral therapy being incriminated least frequently. Reactions are more frequent in atopic individuals,[45] and less frequent in children than adults.[28]

Allergic reactions have been reported in patients who deny prior treatment with penicillin. The usage of penicillins has been so widespread, however, that a strong likelihood exists that everyone has had exposure to them in one form or another even without receiving penicillin therapeutically. Potential sources for contact include foods and milk from animals treated with penicillins, and vaccines to which penicillin is added to suppress bacterial contamination. Medical personnel may be sensitized by topical contact or inhalation during prepa-

ration or administration of the antibiotic. Finally, the parent Penicillium molds are ubiquitous, and their presence or the presence of minute amounts of synthesized penicillin in the environment or on the skin may be sufficient to evoke immunologic recognition.

Reactions may be divided into two major categories, immediate and delayed. Immediate reactions occur within 20 minutes of exposure. The most serious type is anaphylaxis. Its clinical picture is variable. Pruritis or urticaria may constitute the entire reaction. On the other hand, laryngospasm, hypotension, and death may occur. Only 0.1 per cent of all penicillin reactions are anaphylactic, but once anaphylaxis has occurred, mortality ranges from 10 to 25 per cent. Parenteral penicillins are most often incriminated, but anaphylaxis may also follow oral penicillin.

A second type of immediate reaction is the accelerated one. This occurs 20 minutes to 48 hours after exposure. Manifestations include fever, pruritis, and urticaria, but laryngospasm and hypotension infrequently occur. Mortality is distinctly unusual.

Most delayed reactions consist of benign skin rashes. They may take any form or distribution, but classically a maculopapular pruritic eruption develops on the thorax; vesicular, scarlatiniform or bullous lesions may occur, and rarely the full-blown Stevens-Johnson syndrome is seen.

Another type of delayed reaction is a serum sickness-like syndrome which may be especially troublesome following administration of benzathine penicillin. Fever, arthralgia, myalgia, rash, adenopathy, and splenomegaly comprise the major features. Lupus erythematosus preparations may be transiently positive,[32] and on occasion, especially after repeated exposures, periarteritis nodosa may develop. A delayed reaction characterized by confusion and papilledema has been reported.[38]

Penicillin itself is a simple compound and the mechanisms for these varied hypersensitivity reactions are unclear. All or several of the following mechanisms may play a role in allergic penicillin reactions. Degradation of penicillin in aqueous solution results in other compounds which are thought to possess greater potential as allergens. Penicillenic acid is one breakdown product which, via amide or disulfide linkages, can form protein conjugates which may be allergenic. Other similar products include penicilloylamine and penicilloate (Fig. 3). It should be emphasized that these metabolites have not been demonstrated in vivo even though their role is suspect. A mixture of these compounds – the so-called minor determinant mixture (MDM) – has been used in skin testing patients with a history of penicillin allergy.[22]

A second mechanism involves the role of penicillin as a hapten, binding covalently to proteins. Protein binding also takes place at the carboxyl terminal of the open beta-lactam ring, a process known as penicilloylation (Fig. 3). This has been considered to be the major determinant of allergenicity.[25] If the penicilloyl compound is linked in vitro to the epsilon-amino group of lysine, benzyl penicilloyl polylysine can be produced and constitutes a second antigen used in skin testing.

Penicillin for clinical usage, although highly refined, still contains
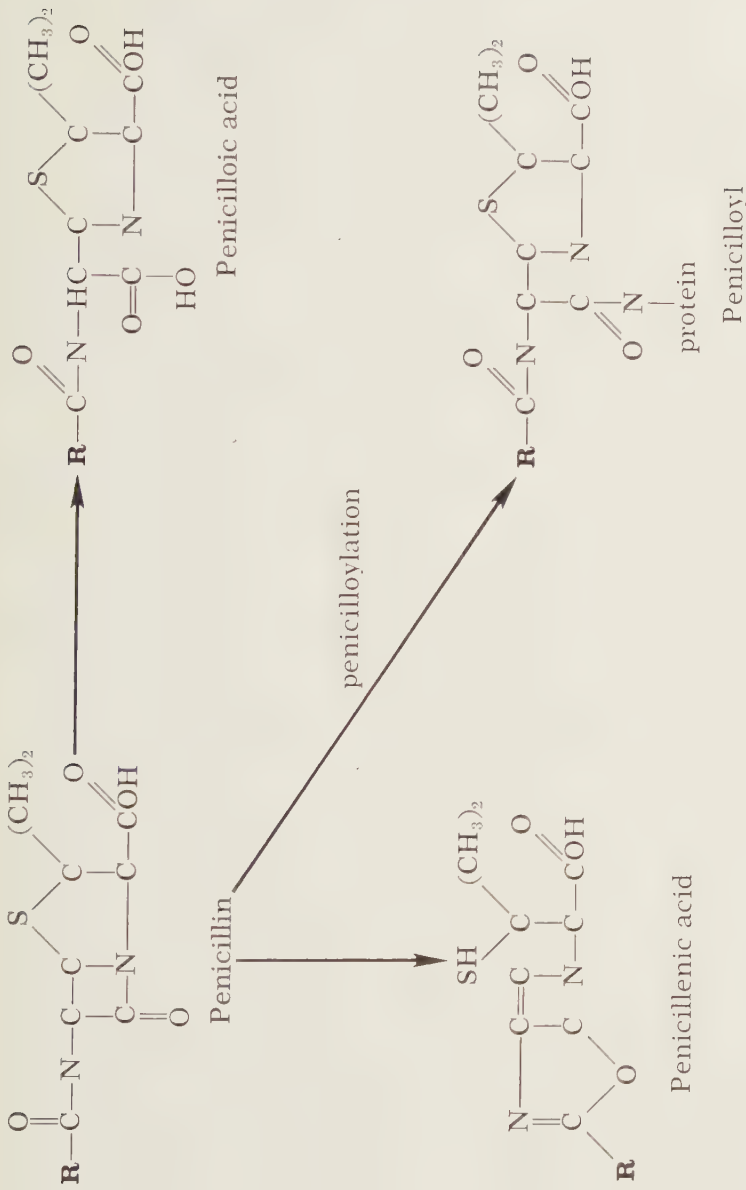
Figure 3. Degradation of penicillin.

traces of impurities. Protein and polypeptide complexes remain from the manufacturing process. These macromolecular compounds may derive from penicillin itself or more likely from the molds and bacteria used in production. Such impurities possess allergenic potential, and their removal by dialysis has been shown to decrease the frequency of penicillin reactions.[14] Even this does not insure freedom from reactions. Antigenic molecular complexes may result from polymerization of purified penicillin when it is kept in solution for long periods of time, as in multiple dose vials.

Immediate reactions probably result from the release of histamine or other mediators, or both, by antigen-antibody interactions. Although the exact antigen is not always clear, the antibody belongs to the class of reaginic antibodies, IgE. These antibodies are skin sensitizing and are responsible for the wheal and flare response following application of skin-testing antigens. Some immediate reactions may be mediated by other antibodies, belonging to the IgG class, which are not skin sensitizing since an immediate reaction may occur with a preceding negative skin test. The mechanisms responsible for delayed reactions are less clear. Antibodies of both the IgG and IgM classes may be involved.[24]

Hemagglutinating antibodies of the IgG and IgM classes develop in a high percentage of patients receiving penicillin, but they usually are clinically insignificant. Their presence or absence is not helpful in predicting immediate reactions. IgM antibodies may be related to skin eruptions and IgG antibodies to the development of hemolysis.[24]

Coombs-positive hemolytic anemia is a rare complication of penicillin therapy.[25, 33, 46] In such cases, during treatment with high doses of penicillin, sensitized red cells are coated in vivo by circulating antipenicillin antibodies. The exact identity of the sensitizing antigen is not known, but the antibody is an IgG immunoglobulin.

Every patient should be questioned in detail regarding a history of penicillin allergy prior to receiving this antibiotic. The type of reaction experienced in the past, the age of the patient at the time, the route by which the drug was administered, and how recently are all important in weighing the chances of an immediate reaction developing. Many patients consider pain at the injection site an allergic reaction. Rashes not related to the drug that develop during an acute illness after penicillin has been given provide confusion. Even with a definite history of an immediate reaction, the passage of time may alter reactivity, so that a second immediate reaction may not occur if a year or more has passed since penicillin was last administered.[9] The wisest and safest course to follow, however, is to accept the history of allergy and select a rational substitute from today's large armamentarium of antibiotics. Penicillin should only be given to a patient with a history of allergy in those distinctly unusual circumstances of life-threatening infections, usually meningitis or endocarditis, in which a highly effective alternative is not available.

The use of skin test antigens to predict which patients with a history of penicillin allergy are most likely to develop immediate reactions has not been highly reliable. Although these methods have been valuable

for investigating mechanisms of penicillin allergy, skin testing in a strictly clinical setting is less contributory. Freshly prepared benzylpenicillin G is quite unsatisfactory as an antigen for skin testing to predict immediate reactions, because false-negative responses are common.[9]

Benzyl penicilloylpolylysine (BPPL) and a MDM have been extensively studied. Negative skin tests with these antigens should essentially exclude an immediate reaction when penicillin is given but delayed reactions may still occur. The rare false negative reactions may be explained by the antigenic determinant not always residing in the BPPL or MDM fractions. False-positive skin tests are frequent and may be due to low levels of reagin or blocking antibodies. A positive skin test indicates an increased likelihood of an immediate reaction, and is often found in patients without a history of allergy, possibly indicating low-grade sensitivity.[21] Disadvantages of skin testing include induction of penicillin sensitivity and anaphylaxis from the procedure itself.[8] In the present state of knowledge and availability of antigens, the decision to use penicillin should not be based on the results of skin testing.

Concomitant corticosteroids and antihistamines may be used to avoid or abort immediate reactions, although their value is unproven. Attempts at hyposensitization progressing from scratch to intradermal to intramuscular test doses seem prudent, in that immediate reactions may be manifest at the site of the test drug rather than systemically, and appropriate measures can be taken to prevent systemic anaphylaxis. After placement of an intravenous fluid line to provide ready access to the vascular system, cautious administration of increasing doses of penicillin can be instituted, beginning with scratch and intradermal test doses and proceeding with subcutaneous and intramuscular doses of 25 units and larger at 30 to 60 minute intervals. If no reaction occurs after an intramuscular dose of 1000 units, further increases are quite safe.

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Phenoxymethylpenicillin (Penicillin V) and Phenethicillin

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Penicillin V (phenoxymethylpenicillin) and phenethicillin (phenoxyethylpenicillin) are closely related analogues of penicillin G (benzylpenicillin) as shown in Figure 1. Their antibacterial spectra are very similar to that of benzylpenicillin, but they are resistant to acid inactivation and are absorbed much better after oral administration. However, stability of an antibiotic to acid does not invariably mean that it will be well absorbed when given by mouth.

Only oral preparations of penicillin V and phenethicillin are available. Their major uses, in general, are as substitutes for oral benzylpenicillin, because they are better absorbed, or instead of some intramuscular forms of benzylpenicillin, such as aqueous penicillin G, procaine penicillin G, or benzathine penicillin, since comparable or superior drug activity may thus be obtained via an oral route.

Penicillin V is prepared by adding its side chain precursor, phenoxyacetic acid, to penicillin fermentation broths to permit the biosynthesis of the antibiotic. Phenethicillin, in contrast, is a "semisynthetic" penicillin prepared by the reaction of the acid chloride of its side chain with the penicillin nucleus, 6-aminopenicillanic acid.

Phenethicillin is a near-racemic mixture of D and L-α-phenoxyethylpenicillin, but the L-isomer accounts for most of its antibacterial activity against Staph. aureus.[18, 26, 31, 35] The D-isomer is only 16 per cent as active as the L-isomer against staphylococci, but data purporting to show some synergy of mixtures of both has been reported.[18, 26, 35] However, against some species—e.g., H. influenzae, N. gonorrhoeae, and N. meningitidis—the L-isomer is clearly the more active.[31] Phenoxymethylpenicillin and phenethicillin are the only phenoxyalkyl penicillins that are now available in the United States. Others in the group, phenoxypropyl, phenoxy-

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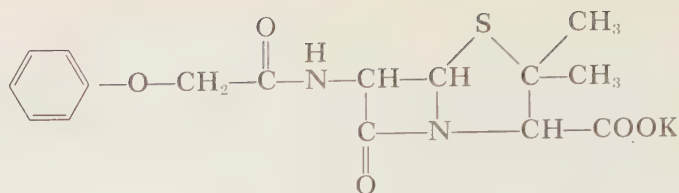
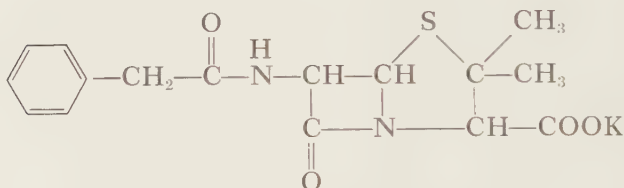Phenoxymethylpenicillin, potassium salt (penicillin V)
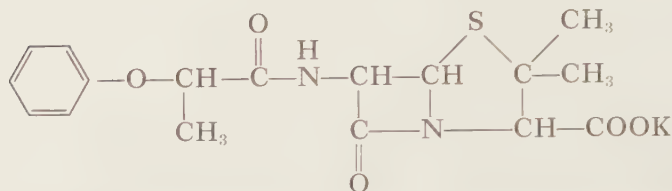
Phenoxyethylpenicillin, potassium salt (phenethicillin)

Benzylpenicillin (penicillin G)

Figure 1.   Structures of potassium salts of three penicillins.

isopropyl, phenoxybutyl, phenoxyisobutyl, and phenoxybenzylpenicil-
lins, are somewhat similar in being acid-resistant, well absorbed after
oral administration, slightly to strikingly less active, and somewhat more
resistant to staphylococcal penicillinase than is benzylpenicillin.[6, 19]
However, their resistance to staphylococcal penicillinase was not great
enough to warrant seriously considering their use in infections due to
penicillinase-producing staphylococci, especially after methicillin, and
later other more effective semisynthetic penicillins, became available.

ANTIBACTERIAL ACTIVITY AND SPECTRUM

The minimum inhibiting concentrations (MIC) of penicillin V and
of phenethicillin for a number of common pathogenic organisms are
listed in Table 1. For most of these organisms, the MIC of penicillin V
is approximately the same as that for benzylpenicillin, although in some
instances, e.g., Neisseria gonorrhoeae, penicillin V is one fourth as
active, four times as much drug being required to inhibit the organism

Table 1. Susceptibility of Some Bacteria to Three Penicillins

| ORGANISM | MINIMUM INHIBITING CONCENTRATION (micrograms per ml.) | | | | | | TOTAL NUMBER OF STRAINS EVALUATED | REFERENCES |
| | PHENOXYMETHYLPENICILLIN | | PHENOXYETHYL-PENICILLIN | | BENZYLPENICILLIN | | | |
	median	(range)	median	(range)	median	(range)		
β-hemolytic streptococci	0.01	(0.0015-3.2)	0.02	(0.0006-6.5)	0.005	(0.0008-0.2)	139	11, 31, 43
D. pneumoniae	0.006-0.012	(0.0015-0.03)	0.012	(0.003-0.06)	0.006	(0.03-0.0015)	42	11, 43
Staph. aureus penicillinase negative	0.02	(0.006-0.08)	0.02	(0.012 0.08)	0.02	(0.006 0.1)	69	31, 43
Staph. aureus	0.2	(0.1-0.8)	0.2	(0.2-0.8)	0.4	(0.4-1.6)	3	46
Staph. aureus penicillinase positive (small inoculum. 100 CFU per ml.)	100	(6.3- >100)	25	(0.4- >100)	>100	(12.4- >100)	54	31
Staph. aureus penicillinase positive								
Enterococci	3.2	(0.8-50)	12.5	(1.6-50)	3.2	(1.6-25)	67	11, 31, 43
N. gonorrhoeae	0.08	(0.001-3.2)	0.16	(0.005-25)	0.02	(0.005-0.4)	29	31
N. meningitidis	1.6	(0.08-3.2)	3.2	(0.16-12.8)	0.2	(0.02 0.2)	8	31
H. influenzae	0.8	(0.2-16)	0.8	(0.2-32)	0.25	(0.05-6.3)	19	11, 43
Proteus mirabilis	100	(32-200)	400	(100- >400)	12.5	(4-200)	21	11, 43
E. coli and "coliforms"	200-400	(50- >400)	>400	(200- >400)	50	(12.5-400)	24	43
Salmonella and Shigella	200-400	(50- >400)	>400	(200- >400)	50	(25-200)	16	43
Salmonella	200	(50-400)	>400	(>400)	100	(50-100)	7	31
Shigella	400	(100-400)	>400	(>400)	200	(100-200)	16	31

CFU. colony forming units

and the MIC being four times as high. In contrast, phenethicillin is only occasionally as active as benzylpenicillin and two to four times as much phenethicillin as benzylpenicillin is required to inhibit many organisms.

One exception in which phenethicillin is more active is against penicillinase-producing strains of Staphylococcus aureus when comparatively small inocula are used (Table 1). However, when large inocula are used, which many investigators believe to be more realistic, phenethicillin does not appear to be active enough for clinical use.[15]

Thus, the spectrum of organisms susceptible to penicillin V and phenethicillin is essentially the same as that of benzylpenicillin: most gram-positive cocci, with the exception of penicillinase-producing staphylococci, as noted. Although the MIC of penicillin V for Escherichia coli and Proteus mirabilis is sufficiently high to suggest that they are "out of its spectrum" of activity because those concentrations are not ordinarily achieved in serum, it should be noted that those concentrations are sometimes achieved in urine on standard doses (vide infra).

CLINICAL PHARMACOLOGY

Greater amounts of penicillin V and of phenethicillin are absorbed and appear in serum after oral administration than of benzylpenicillin

Table 2. *Approximate Serum Concentrations of Some Penicillins Following Oral or Intramuscular Administration*

PREPARATION	ROUTE	RELATION TO FOOD	DOSE (mg.)	SERUM CONCENTRATION (micrograms per ml.) AT INDICATED TIME AFTER DOSE					REFERENCE
				½ hr	1 hr	2 hr	4 hr	5 hr	
Phenoxymethyl-	p.o.	before	500	3.4	2.2	0.9	–	0.05	30
penicillin	p.o.	after	500	2.2	4.6	1.5	–	0.3	30
	p.o.	before	250	–	1.5	0.4	0.03	–	25
	p.o.	not stated	250	–	2.2	0.8	0.2	–	6
	p.o.	before	250	2.1	1.8	0.6	–	–	10
	p.o.	after	250	0.5	0.6	0.6	–	–	10
	p.o.	before	165	–	0.3	0.7	0.1		43
Phenethicillin	p.o.	before	500	4.0	4.3	1.4	–	0.1	30
	p.o.	after	500	2.4	4.5	2.1	–	0.5	30
	p.o.	before	250	–	4.1	1.2	0.1	–	25
	p.o.	not stated	250	–	3.4	2.1	0.3	–	6
	p.o.	before	268	2.8	3.8	1.1	–	–	10
	p.o.	after	268	1.2	1.8	1.1	–	–	10
	p.o.	before	180	–	6.4	1.8	0.4	–	43
Benzylpenicillin	p.o.	before	600	0.2	0.7	0.6	–	0.2	30
potassium	p.o.	after	600	0.1	0.4	0.3	–	0.4	30
	p.o.	before	157	–	0.9	0.3	0.1	–	13
Benzylpenicillin	i.m.	after	500	3.9	4.5	3.1	–	0.8	30
aqueous	i.m.	after	240	3.4	3.2	0.8	–		25
	i.m.	after	250	4.3	4.9	2.5	0.8	–	9
Benzylpenicillin procaine	i.m.	not stated	360	0.33	–	–	0.41	–	48

– = Data not available.
1,000,000 units benzylpenicillin equals 600 mg.

Table 3.   *Recovery of Various Penicillins in Urine*

PREPARATION	ROUTE	RELATION TO FOOD	DOSE (mg.)	TOTAL (MG.) AND PER CENT OF DOSE RECOVERED IN URINE IN FIRST 5 TO 8 HOURS			REFER-ENCE
				5 hr	6 hr	8 hr	
Phenoxymethyl-penicillin	p.o.	before	500	160 (32%)			30
	p.o.	after	500	121 (24%)			30
	p.o.	–	250		65 (26%)	65 (26%)	7
Phenethicillin	p.o.	before	500	190 (38%)			30
	p.o.	after	500	150 (30%)			30
	p.o.	–	250		58 (23%)	81 (32%)	7
Benzylpenicillin	p.o.	before	600	53 (9%)			30
		after	600	28 (5%)			30
Benzylpenicillin (aqueous)	i.m.	after	500	240 (48%)			30

(Table 2). However, after each of these three penicillins, when given orally, serum antibiotic concentrations are much higher than those found after intramuscular injections of the same number of units of procaine penicillin G and, except for benzylpenicillin, they approach those obtained with intramuscular aqueous benzylpenicillin (Table 2). The relation between time of ingestion of drug and food influences the "peak" concentration of penicillin V and phenethicillin only slightly, but that of benzylpenicillin is affected somewhat more (Table 2).

Even though penicillin V and phenethicillin are better absorbed than benzylpenicillin, only 23 to 38 per cent of the administered dose of those antibiotics appears in the urine (Table 3). In contrast 80 to 100 per cent of intravenously administered benzylpenicillin appears in the urine.

The rapid renal excretion of penicillin V and phenethicillin is similar to that of benzylpenicillin. Tubular secretion ordinarily accounts for most of the renal clearance of these antibiotics, and it can be blocked with oral probenecid (Benemid), leading to higher (often double the peak) and more sustained serum concentrations.

The protein binding of penicillin V and of phenethicillin is grossly comparable to that of benzylpenicillin and is not a significant factor to be considered.[6]

PREPARATIONS AND DOSAGES

Both drugs are generally available as the potassium salts.

PENICILLIN V.   Tablets each containing 125, 250, or 300 mg. are available (125 mg. equals 200,000 units). Dried powders for reconstitution and oral suspensions, for use primarily in infants and children, are available and usually contain 90, 125, 180, or 250 mg. per 5 ml. (teaspoonful). "Drops" containing 12.5 mg. per drop are also available. A liquid preparation of the benzathine (rather than potassium) salt is available, containing 180 mg. per 5 ml.

PHENETHICILLIN. Tablets (125 or 250 mg. each) and liquid preparations containing 125 mg. per 5 ml. (teaspoonful) are available. "Pediatric drops" contain 125 mg. per dropperful—0.6 ml.

The "usual" dose depends on the infection being treated. For adults with most infections for which these antibiotics are indicated, the dose is 125 to 250 mg. every 6 hours. For infants and children 5 to 25 mg. per kg. every 6 to 8 hours is recommended.

Larger doses are prescribed when these preparations are used in the treatment of bacterial endocarditis (3.6 to 9 gm. per day has been used), osteomyelitis, lung abscess, and gonococcal urethritis. Many experts feel that oral penicillins should not be used for any infections where larger doses are needed, because there may be questions about the patient's reliability in taking the medication, absorbing it, and developing diarrhea—problems that are less troublesome or nonexistent with the alternative parenteral medications. However, if penicillin V or phenethicillin is to be used in larger doses in adults, it is usually at 500 to 1500 mg. every 4 to 6 hours and often supplemented with probenecid, 500 mg. by mouth every 6 hours (not necessary if there is renal failure).

Duration of treatment varies with the indication. For streptococcal pharyngitis and otitis media, 10 days is recommended (if there is a prompt response). In bacterial endocarditis, 2 weeks have been adequate for endocarditis due to susceptible alpha-hemolytic streptococci but longer treatment, up to 6 weeks, is generally recommended.

INDICATIONS

Phenoxymethylpenicillin is a suitable agent in the following situations providing the etiologic agent is susceptible to generally achievable concentrations: streptococcal pharyngitis and tonsillitis, otitis media, bronchitis, or pneumonia due to Diplococcus pneumoniae or penicillinase-negative Staph. aureus, prophylaxis of rheumatic fever, pyodermia due to penicillinase-negative Staph. aureus, streptococcal cellulitis, and gonococcal urethritis. In gonococcal urethritis, neither phenoxymethylpenicillin nor phenethicillin is nearly as desirable as benzylpenicillin or ampicillin. It is also indicated in most other infections, e.g., sinusitis, caused by D. pneumoniae, beta hemolytic streptococci, or penicillinase-negative Staph. aureus.

Penicillin V has been used as the only oral form of penicillin for successfully treating bacterial endocarditis due to Strep. viridans[16, 17, 37, 40, 45] and as a supplement to intramuscular penicillins[17] in endocarditis when the intravenous route could not be used. However, in endocarditis it is important to establish in the laboratory that the organism is sufficiently sensitive to the penicillin being considered,[12] and only then may either phenoxymethylpenicillin or phenethicillin be indicated.

Either penicillin V or phenethicillin may be used for short term "prevention" of bacterial endocarditis associated with tooth extraction in patients with rheumatic or congenital heart disease. Therapy (1.0 gm. every 4 to 6 hours) should be begun 1 or 2 hours before the extraction and

continued for 24 to 72 hours. Patients who have received penicillin for 24 or more hours before a tooth extraction should probably have a different antibiotic used for prophylaxis at the time of the extraction.[13]

Phenethicillin may be used in all of the above situations, but its lower activity (see Table 1) against N. gonorrhoeae makes it much less desirable than benzylpenicillin, ampicillin, or even phenoxymethylpenicillin. Its lower activity suggests that it rarely will be the drug of choice in endocarditis, even though good results have been reported (vide infra). Its higher cost and decreased activity against many organisms makes it less desirable than oral benzylpenicillin or phenoxymethylpenicillin in most situations, in spite of its good absorption.

RESULTS

No comparative study showing a significant advantage of one form of phenoxymethylpenicillin over another (acid, potassium salt, benzathine salt) has been reported. Most of the results to be described have been performed with the acid or potassium salt.

In streptococcal carriers, oral phenoxymethylpenicillin was comparable to benzylpenicillin.[17] It has been previously shown, in the prophylactic use of oral benzylpenicillin to prevent recurrent streptococcal pharyngitis, that a larger proportion of "failures" (up to five times as many) occurred than had after intramuscular therapy with long-acting preparations of benzylpenicillin.[28, 29, 49] One would, therefore, also expect intramuscular prophylaxis to be superior to phenoxymethylpenicillin or phenethicillin.

In bacterial endocarditis (mostly due to Strep. viridans), cure rates well above 90 per cent have been reported,[14, 17, 37, 40, 45] results certainly no worse than those with parenteral benzylpenicillin (75 to 88 per cent cures) reported or summarized by others.[22, 24, 27]

Comparative evaluation of phenoxymethylpenicillin with alternative agents is not as well established with other infections, but the results are certainly satisfactory in otitis media,[5] bronchitis, and pneumonia[3, 21, 33, 38] when caused by susceptible organisms.

Experience with phenethicillin is much less extensive than with phenoxymethylpenicillin, but satisfactory results have been reported when it was used for pharyngitis, or tonsillitis due to beta-hemolytic streptococci,[16, 39, 42, 44] otitis media,[5, 34, 39, 42, 44] bronchitis,[16, 42, 44] sinusitis,[16, 42, 44] pneumonia,[7, 16, 39, 44] and cellulitis, pyoderma,[16, 36, 39] osteomyelitis,[16] pyogenic arthritis,[16] and endocarditis due to alpha-hemolytic streptococci.[8, 16, 23] Results in other forms of endocarditis with positive blood cultures were less favorable: five of eight patients survived.[8, 16, 23] Although few studies comparing the efficacy of phenethicillin with alternative drugs are available, phenethicillin yielded results equally favorable to benzylpenicillin in the treatment of otitis media,[5, 34] although in another study the response was thought to be slower.[32] In gonococcal urethritis the results were less favorable with phenethicillin than with benzylpenicillin.

ADVERSE EFFECTS

As has been noted with other oral penicillins, diarrhea may be expected in about 10 per cent or more of patients receiving 4 gm. or more per day of phenoxymethylpenicillin, but Gold noted no diarrhea in 100 patients receiving phenethicillin, including 11 being treated for endocarditis.[16] Reliable data are lacking on the incidence of allergic reactions to these antibiotics, but it is probably less than occurs following other penicillins—if they are given parenterally. Allergic reactions to phenoxymethylpenicillin and to phenethicillin are probably much less frequent than following ampicillin, which appears to be more allergenic than other penicillins.[2, 41]

Although not strictly an adverse effect, the change in oral flora that occurs following prolonged administration (repopulation with penicillin-resistant organisms) may represent a special hazard for patients with valvular heart disease who are to have teeth extracted.[13]

SUMMARY AND CONCLUSIONS

Phenoxymethylpenicillin and phenethicillin are penicillins with antibacterial activities and spectra very similar to those of benzylpenicillin. They are more resistant to acid inactivation and are better absorbed after oral administration (the only form available) which at times makes them preferable to benzylpenicillin. However, against some organisms the activity of phenethicillin is somewhat less than that of benzylpenicillin and phenoxymethylpenicillin, thus nullifying an advantage gained by good or superior absorption.[20, 30] Phenethicillin has not been shown to be superior to phenoxymethylpenicillin for any infection. When cost is no object, phenoxymethylpenicillin appears to be the preferable oral penicillin for most infections caused by susceptible organisms in which oral treatment is desired. Appropriate attention must be given and laboratory tests made in bacterial endocarditis to be sure that phenoxymethylpenicillin itself is adequately active; the assumption that it is equivalent to benzylpenicillin should not be made in this situation.[12]

When cost is an important factor, the possibility of using oral benzylpenicillin rather than phenoxymethylpenicillin should be considered. Prices quoted by mail order drug suppliers reveal that "national brand" phenoxymethylpenicillin is only 1.3 times as costly as "national brand" benzylpenicillin, making the former ultimately much more desirable, because of its superior absorption. However, "generic" benzylpenicillin costs only one seventh as much as phenoxymethylpenicillin, but produces less than one half the serum activity (about one fifth to one seventh the absolute concentration) of phenoxymethylpenicillin (Table 2), perhaps making some difference (less than one third) in the cost on the basis of activity. But against some common pathogens (e.g., streptococcus, staphylococcus, pneumococcus) the absorption of oral benzylpenicillin after a 600 mg. dose produces what appears to be adequate serum activity, suggesting that it may be less costly treatment in those infections.

Because the local costs of "generic" products vary greatly, it is impossible to generalize on whether this saving would be passed on to the patient.

Failure of the patient to take oral medication at home is a common cause of treatment failure in most of the infections mentioned here,[1] probably more important than are the relative differences in absorption described. Insisting that the patient (or the parent of a sick child) record the time each dose is administered, and that the record of drug administration be brought in on follow-up visits, frequently makes a big difference in amount of drug ingested and in the therapeutic response. For pediatric suspensions requiring refrigeration, the refrigerator door is a convenient place to scotch tape a calendar on which such information can be recorded.

Strict attention to such details as getting the drug ingested, the time relation of antibiotic ingestion to meals and appropriate use of probenecid are required if oral penicillins are to be used in serious infections. Wherever these variables cannot be controlled, parenteral administration of the appropriate antibiotic is preferable.

SYNONYMS AND TRADE NAMES OF DRUGS

Phenoxymethylpenicillin: penicillin V, V-cillin, Pen-Vee, and as the potassium salt: Compocillin VK, Pen-Vee K, V-cillin K.

Phenethicillin: D-L phenoxyethylpenicillin, Syncillin, Maxipen, Darcil, Semopen, Alpen, Broxil, Chemipen, Dramacillin S.

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Methicillin: Critical Appraisal after a Decade of Experience

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Methicillin first became available for general use in the fall of 1960. As the first penicillin which was resistant to staphylococcal penicillinase, it represented a major advance in antistaphylococcal therapy, and hence enjoyed instant clinical popularity.[29, 32, 41, 50] A decade later, and after the subsequent introduction of other penicillinase-resistant penicillins, it is appropriate to critically evaluate the therapeutic indications and limitations of methicillin.

CLINICAL PHARMACOLOGY

Spectrum of Antimicrobial Activity

The minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) of a given antimicrobial agent against specific bacteria is a common in vitro measure of antibacterial activity. The MIC is that concentration of antibiotic which inhibits the growth of a standardized inoculum of bacteria. To determine the MBC, subcultures from tubes demonstrating growth inhibition (MIC) are placed on fresh culture media to ascertain residual growth potential. Two technical points are worth emphasis. The number of bacteria challenged (the inoculum) with a given antibiotic concentration is an important variable, because some antibiotics decrease in efficacy with high inocula. Likewise, the presence or absence of protein in the culture medium may influence data interpretation, especially if extrapolated to in vivo situations.

The sensitivity or resistance of a particular bacterium to a specific antibiotic, as judged by an MIC determination, is a laboratory guideline of antibacterial spectrum but does not necessarily imply in vivo susceptibility. In vivo responsiveness is also influenced by attainable serum levels, distribution, metabolism, and excretion of the antibiotic. In general, laboratory interpretation of susceptibility is based upon usual serum antibiotic concentrations. It is common to compare the in vitro activity (MIC) of a new antibiotic against the activity of a proven antibiotic for the organism in question. For example, penicillin G is more active (lower MIC) against D. pneumoniae than methicillin in vitro. The molecular weights of the two penicillins differ, their clinical dosages vary, and their in vivo pharmacology differs so that such in vitro MIC comparisons are at best only crude guidelines. The primary value of MIC and MBC determinations, in the evaluation of an antibiotic, is to outline the spectrum of antibacterial activity.

MIC determinations with methicillin demonstrate significant activity against penicillinase-producing and non-penicillinase producing staphylococci (Table 1).[1, 22, 39, 50] Methicillin is also active against other gram-positive and gram-negative cocci, with the notable exception of Streptococcus fecalis (Enterococcus). The gram-negative rods are uniformly resistant. With mutually susceptible organisms, methicillin is "less potent," on a strictly weight basis, than penicillin G. The large doses of methicillin employed clinically make the significance of this difference disputable.

Table 1. *Comparison of the Minimum Inhibitory Concentration* *of Penicillin G and Methicillin Against Selected Organisms*[31, 39]

ORGANISM	NO. OF STRAINS	PENICILLIN G MIC (micrograms per ml.) Range	Median	METHICILLIN MIC (micrograms per ml.) Range	Median
Staphylococcus aureus					
Penicillinase producer	36	50–>200	>200	1.6–6.3	3.1
Non-penicillinase producer	20	0.1–0.4	0.2	3.1	3.1
Staphylococcus albus					
Penicillinase producer	116	0.4–>100	>100	0.4–100	3.1
Non-penicillinase producer	59	0.04–1.6	0.04	0.2–12.5	1.6
Streptococcus pyogenes					
Group A	30	0.0025–0.1	0.005	0.2–0.4	0.4
Group B and C	15	0.01–0.1	0.02	0.2–3.1	0.4
Group C	12	0.005–0.04	0.01	0.4–12.5	0.4
Streptococcus viridans	19	0.1–1.6	0.8	0.2–6.3	3.1
Streptococcus fecalis (Enterococcus)	27	1.6–3.1	3.1	≥ 100	> 100
Neisseria gonorrhoeae	2	0.02–0.2		0.8	
Hemophilus influenza	10	0.8–3.1	1.6	6.3–25.0	25.0
Proteus mirabilis	20	6.3–100	12.5	> 100	> 100
Proteus vulgaris	2	> 100		> 100	
Escherichia coli	17	> 100		> 100	
Klebsiella pneumoniae	10	> 100		> 100	

ᵇMICs performed in broth without added protein

The in vitro antibacterial activity of methicillin is not influenced by inoculum size.[22] Likewise, there is little difference between the MIC and MBC of susceptible bacteria.[47]

Of greatest clinical interest is the activity of methicillin against penicillinase-producing staphylococci (Table 1). The MIC range in broth cultures is 1.6 to 6.25 micrograms per ml. The rare methicillin-resistant staphylococcus is defined primarily by an MIC of ≈ 12.5 micrograms per ml.[17]

Methicillin Serum Concentrations

For serious staphylococcal infections, such as endocarditis or acute osteomyelitis, it is desirable to achieve serum concentrations that are two to four times the MIC, and to maintain such levels for at least part of the interval between doses.

Effective serum levels of methicillin are not obtainable by oral administration.[50] However, significant serum concentrations are achieved by intramuscular or intravenous administration.[50] The serum concentration after intramuscular administration peaks at 30 minutes (Table 2). By 5 hours the serum concentration is very low.[50] Repeating the same dose (1 gm.) intramuscularly every 4 hours produces essentially the same blood levels as indicated in Table 2, with no evidence of accumulation of the drug.[15] More than two-thirds of an intramuscular dose is recoverable in the urine within 4 hours.[50] The renal clearance of methicillin is 4 to 6 times greater than the creatinine clearance.[34] Probenecid (0.5 gm. every 6 hours) significantly increases and prolongs serum methicillin levels.[50]

Examples of the range and mean serum concentration after intravenous methicillin are shown in Table 3.[15] Again, the rapid clearance is evident with insignificant levels after 3 hours. Only slight serum accumulation occurs with repeated intravenous doses at 4 hour intervals.

Both intramuscular and intravenous administration are well tolerated. The lability of methicillin in acid solutions is pertinent in regard to intravenous therapy. The pH of intravenous solutions is generally acid; for example, the pH of five per cent dextrose in water varies between 4.5 and 6.5.[36] The effect of common intravenous solutions on methicillin stability is summarized in Table 4.[52] If the pH of five per cent dextrose in water is adjusted to 7.2 by adding 3 mEq. of $NaHCO_3$

Table 2. *Average Serum Levels and Urinary Excretion of Methicillin in Normal Volunteers After a Single Intramuscular Dose of One Gram*[50]

	SERUM METHICILLIN (micrograms per ml.) HOURS AFTER DOSE					PER CENT DOSE EXCRETED IN 6 HOURS
	1/2	1	2	3	5	
Average	16.0	13.8	7.3	3.8	1.1	66.6
± SD	9.0	9.6	4.7	1.2	0.7	6.7

DAVID N. GILBERT, JAY P. SANFORD

Table 3. *Serum Concentrations (micrograms per ml.) of Methicillin After Intravenous Single Doses*[15]

NO. OF SUBJECTS	DOSE (mg.)	TIME IN HOURS				
		1/4	1/2	1	2	3
5	2000	72.4* (57–88)‡	45.0 (32–68)	18.8 (14–29)	4.8 (3.3–8.5)	0.9 (0.5–1.2)
5	1000	32.5 (26–38)	17.5 (16–20)	7.32 (5.4–11)	1.97 (1.2–3.6)	
5	500	16.2 (12–24)	10.8 (7–19)	3.4 (2.6–4.5)	1.1 (0.7–1.9)	
5	250	7.3 (5.9–9.8)	3.5 (3.0–4.4)	1.6 (1.0–2.9)	0.1 (0.3–0.5)	

*Mean
‡Range

Table 4. *Maximum Time Period Methicillin Should be Used or Allowed to Stand at 25° C. When Added to Various Intravenous Solutions*[52]

SOLUTION	UTILITY TIME (HOURS)	
	1 gm. Methicillin per 500 ml.	5 gm. Methicillin per 500 ml.
5 per cent dextrose in saline	2	8
5 per cent dextrose in water	2	8
10 per cent dextrose in water	2	4
Normal saline	4	8
Ringer's lactate	4	12

(approximately 3.5 ml. of standard 44.5 mEq. ampule), methicillin remains stable for over 24 hours.[29] The problem of acid hydrolysis is easily avoided by infusing the desired dose (for example, 2 gm. in 50 ml.) over a 20 to 30 minute interval. To meet the goal of a serum concentration that is two to four times higher than the MIC during at least part of the therapeutic time interval, for serious staphylococcal infections a dosage of 2 gm. intravenously every 4 to 6 hours is recommended. Lower doses will suffice for the more susceptible pneumococci and streptococci.

Distribution

Like other penicillins, no significant cerebrospinal fluid methicillin concentrations are found in normal individuals.[49] Methicillin concentrations essentially equal to simultaneously obtained serum levels are found in noninfected pleural, pericardial, and ascitic fluid.[63] In patients with normal liver function, therapeutically effective levels are achieved in the bile.[23] Experimental animal studies demonstrate high concentrations of methicillin in lymph[29] and prostatic fluid.[15] Although methicillin concentrations are not reported, penicillin and nafcillin levels in infected joints were equivalent to simultaneous serum concentrations.[13] This apparent easy diffusibility of methicillin is usually attributed to its relatively low degree of serum protein-binding.

PROTEIN-BINDING: EXTENT AND SIGNIFICANCE

While the clinical significance of the serum protein binding of penicillin is still uncertain, it is reasonable to include protein-binding as an important pharmacologic variable.[35, 46] Antibiotics characteristically bind to serum protein with a resultant increase in solubility. Protein-binding is a dynamic process with a constant proportion of drug in the free or unbound state:

Protein + Antibiotic ⇌ Protein-Antibiotic Complex

As free antibiotic is removed by kidney, liver, or tissue, more antibiotic is released from the complex to maintain a constant proportion of free antibiotic. Thus, serum protein-binding does not influence the eventual utilization of all the antibiotic present in serum. However, serum protein-binding is a major factor in determining the amount of free antibiotic available *at any given point in time*. It is only the free antibiotic which is capable of antimicrobial action.

The distribution of the protein-antibiotic complex depends on the distribution of the binding protein, and thus tends to remain intravascular. Glomerular filtration is essentially limited to the free antibiotic. Even highly bound antibiotics can be rapidly cleared by active tubular secretion of unbound drug. Thus, if two similar penicillins are compared and one is more highly protein-bound than the other (assuming identical absorption and excretion), the more highly bound penicillin should:[35] (1) have higher total serum concentrations with the same or less free antibiotic, (2) last longer in the serum and have a slower renal excretion, and (3) be less well distributed in the extravascular space.

As far as is known, penicillins bind only to serum albumin. The serum binding of methicillin as compared to other penicillins is indicated in Table 5.[35] Only ampicillin has a lower degree of protein-binding than methicillin. The MICs of various penicillin antibiotics are increased when determined in serum, and the magnitude of the increase depends on the degree of protein-binding (Table 5).[35]

Protein-binding also occurs in vivo. When free and total serum antibiotic concentrations were measured in healthy volunteers after intramuscular injection of penicillin analogues, methicillin produced free serum concentrations that were 10 times higher than all other penicillinase-resistant penicillins.[35]

Table 5. *Extent of Serum Protein-Binding of Penicillin Analogues and Effects on MIC Determinations*[35]

PENICILLIN ANALOGUE	PER CENT PROTEIN-BINDING ± SD	MIC* (micrograms per ml.)	
		Broth	Serum
Penicillin G	64.4 ± 8.0	0.04	0.07
Penicillin V	78.5 ± 6.3	0.04	0.10
Ampicillin	22.5 ± 13.7	0.15	0.15
Methicillin	37.3 ± 7.9	1.5	1.5
Nafcillin	89.9 ± 1.5	0.3	2.5
Oxacillin	94.2 ± 2.1	0.3	4.25
Cloxacillin	95.2 ± 0.5	0.2	5.5
Dicloxacillin	97.9 ± 0.6	0.1	5.5

*Test organism is a penicillin G-sensitive staphylococcus.

It is clear that serum protein-binding may not accurately reflect conditions at the site of active infection. The influence of proteinaceous inflammatory exudates and tissue granulomata on antibiotic availability is largely unknown.[46]

Thus, it is reasonable to include per cent serum protein-binding as a significant variable in the clinical pharmacology of penicillin analogues. The dosage schedules of highly bound penicillinase-resistant penicillins are adjusted to achieve serum concentrations of free drug well in excess of in vitro broth MIC values.

EFFECT OF RENAL FAILURE

In volunteers with normal renal function, 70 to 80 per cent of an intramuscular dose of methicillin appears in the urine.[50] In severely oliguric patients, there is a significant prolongation of the serum disappearance time of methicillin.[14] A similar effect is reported for penicillin G and ampicillin.[13, 14, 15] In patients with renal insufficiency, it is recommended that methicillin dosage be reduced. This is accomplished by increasing the interval between doses to 2 gm. intravenously every 8 to 12 hours instead of every 4 hours.

Although the penicillins do cross dialysis and peritoneal membranes, the extent and rate of passage is small.[13, 15] Serum levels of methicillin after intravenous administration in azotemic patients are not affected significantly by peritoneal dialysis or hemodialysis. Thus, there is no need to adjust methicillin dosage during peritoneal dialysis or hemodialysis.

LABORATORY DIFFERENCES BETWEEN METHICILLIN AND OTHER PENICILLINASE-RESISTANT PENICILLINS

This is a subject of some current controversy. Some authors recommend methicillin as the drug of choice for severe staphylococcal infections.[29] Others feel that nafcillin or oxacillin should be used and that methicillin can be dropped from the therapeutic armamentarium.[26] Finally, some reviewers indicate no significant differences between the available drugs.[32, 47] There are several reasons for such divergent opinions. Most stem from extrapolation of in vitro or animal pharmacologic data to clinical infections. It is convenient to divide the laboratory differences into theoretical and practical aspects, and then to turn to clinical results.

Theoretical Differences

As judged by MIC determinations, the antimicrobial spectrum of all the penicillinase-resistant penicillins is nearly identical.[32] Milligram for milligram, nafcillin, oxacillin, and cloxacillin are roughly four times more active than methicillin against penicillin-resistant Staphylo-

coccus aureus. Similarly, penicillin G is far more active against suscep-
tible organisms on a weight basis than methicillin, nafcillin, oxacillin,
or cloxacillin.

However, as discussed above, methicillin is the least protein bound,
about 40% (Table 5).[5] Nafcillin is 90 per cent, oxacillin and cloxacillin
are 95 per cent, and dicloxacillin is 98 per cent protein-bound. Theo-
retically, methicillin has the advantage of greater amounts of free drug
at any instant. However, because of its rapid excretion, it is necessary
to give frequent large doses to maintain adequate serum concentrations.
In contrast, the higher degrees of protein-binding result in longer serum
half-lives of the other drugs. These differences are reflected in the
dosages recommended for severe staphylococcal infections (in adults):
methicillin 6 to 24 gm. per day, and nafcillin 3 to 12 gm. per day.[60] At
the same time, the volume of distribution and diffusion into serous
cavities of methicillin is greater than that observed with oxacillin,
nafcillin, cloxacillin, or dicloxacillin.

All of the semisynthetic penicillins are active in the presence of
high concentrations of penicillinase-producing staphylococci.[32] There
is no reported difference in the in vitro tendency toward development
of bacterial resistance.

The importance of many of these interacting theoretical laboratory
variables is reflected in "ED_{50}" values. The ED_{50} is that dose of a given
antibiotic which will cure (prevent death) 50 per cent of experimental
animals infected with a particular organism. In experimental perito-
nitis in mice due to Strep. pyogenes, Diplococcus pneumoniae, and non-
penicillinase-producing Staph. aureus, penicillin G had an ED_{50} lower
than methicillin or nafcillin.[65] Using penicillinase-producing Staph.
aureus as the infecting organism, nafcillin and methicillin had similar
ED_{50} values when given in two intramuscular injections.[65] With a single
intramuscular dose, nafcillin appeared superior, but this apparent
superiority probably reflects the rapid excretion of methicillin.[64] These
results again indicate the need for larger, more frequent doses of methi-
cillin, but provided these requirements are recognized, methicillin and
nafcillin appear comparable in effectiveness against experimental
infections in mice. They also illustrate that differences in ED_{50} dosages
are considerably less than the marked differences in MICs in broth
cultures.

Practical Differences

Methicillin can only be administered parenterally. The other four
penicillinase-resistant penicillins are absorbed orally. However, oral
administration is not recommended for the treatment of severe staphy-
lococcal infections.

Oxacillin and nafcillin are reported to share with methicillin the
instability in acid fluids used for parenteral therapy. Nafcillin is perhaps
more sensitive in this regard.[60]

Methicillin, nafcillin, and oxacillin are supplied as sodium salts.
Using maximum daily doses, 12 gm. of methicillin contains 37 mEq.
of sodium, and 6 gm. of oxacillin or nafcillin contains nearly 14 mEq.
of sodium.

CLINICAL EXPERIENCE

Final assessment of the therapeutic value of an antimicrobial agent must be based upon clinical experience. Comparison of the clinical efficacy of two or more pharmacologically similar agents is essential, but the design and evaluation of studies which permit detection of subtle differences is difficult. In practice, methicillin is employed primarily as an antistaphylococcal agent. While methicillin is indicated only for infections caused by penicillinase-producing staphylococci, in some hospitals such strains have accounted for more than 80 per cent of staphylococcal infections.[1, 6, 62] Hence the use of a penicillinase-resistant penicillin in most instances of significant staphylococcal infection is justified. Because of difficulties in differential diagnosis, methicillin is often employed in patients with pneumococcal or group A streptococcal infections when staphylococci also are suspected.

In the clinical evaluation of antistaphylococcal agents, consideration of host factors such as age, underlying disease processes, type of infection, and adjunctive therapy such as surgical drainage is necessary. For example, in adults with staphylococcal bacteremia, mortality increased from about 35 per cent in patients aged 20 to 30 years to near 70 per cent in those aged 70 to 80 years.[27] Evaluation in self-limited soft-tissue infections is obviously of less value than evaluation based upon treatment of staphylococcal bacteremia, pneumonia, or endocarditis. Bryant et al. evaluated the effectiveness of oxacillin in staphylococcal skin infections in a group of students aged 6 to 12 years.[9] Thirty-one patients treated with oxacillin and hot soaks were compared with a similar number of patients, matched according to size of furuncles, and treated only with hot soaks. Mean healing time for furuncles in patients treated with oxacillin was 7.0 days, compared with 6.0 days in the "control" group. These data illustrate the difficulty in evaluation of self-limited infections, since without a comparison of "untreated" children, the results would have been considered as excellent.

The efficacy of the semisynthetic penicillins, primarily methicillin, in patients with serious staphylococcal infections, such as bacteremia, pneumonia, or endocarditis, is summarized in Table 6. Based upon the experiences illustrated, most investigators conclude that no significant differences exist between the clinical results obtained with various semisynthetic penicillinase-resistant penicillins. These results are comparable to those achieved with vancomycin or cephalothin. Methicillin also is reported effective in the treatment of pneumococcal pneumonia and group A streptococcal infections.[16, 36]

While the newer semisynthetic penicillins have both oral and parenteral forms, are more stable in acid solutions, and require less drug, methicillin administration is no more expensive to the patient and may achieve better distribution in the body. Because of the experience gained with methicillin, we continue to use it as the primary antibiotic in the management of serious staphylococcal infections. We feel that, provided the necessary dosage adjustments are made, the currently available semisynthetic penicillinase-resistant penicillins are essen-

Table 6. *Antibiotics in Serious Staphylococcal Infections*

ANTIBIOTIC	REFERENCE	NO. OF PATIENTS	MORTALITY
Methicillin	1	22	27%
	38	7	29%
	57	10	10%
	51	63	40%
	16	28	36%
	58	19	32%
Oxacillin	57	4	25%
	33	63	35%
Nafcillin	38	10	40%
	18	43	37%
Vancomycin	30	33	40%
	19	34	29%
	58	6	33%

tially interchangeable. Certainly, on the basis of the reported clinical experience with methicillin, it seems difficult to justify the conclusion of Hoeprich that methicillin has no place in the 1970 formulary.[26]

METHICILLIN-RESISTANT STAPHYLOCOCCI

Only 2 years after the introduction of methicillin, the first methicillin-resistant strains were detected in England.[28] Surveillance of British hospitals showed a gradually increasing prevalence from 0.06 per cent of staphylococcal isolates in 1960 to 4.11 per cent in 1969.[17, 42] Subsequently, methicillin-resistant Staph. aureus were reported from many European countries and South Africa.[14, 21, 27]

In the United States, methicillin resistance was detected first in strains of coagulase-negative Staph. epidermidis.[31] To date, roughly 40 to 50 isolations of resistant coagulase-positive Staph. aureus have been reported from scattered hospitals, first in Seattle, Washington, and then from many other hospitals.[5, 7, 10, 12]

The laboratory characteristics of resistant strains are pertinent. Many are in phage group III, but often they are not typable.[1, 5, 12] Methicillin-resistant isolates are heterogeneous, with the largest proportion of cells methicillin-sensitive.[54, 59] The resistant organisms grow much slower than the sensitive ones. The slow growth presents a practical problem of laboratory detection. To overcome this, it is suggested that the drug sensitivity of staphylococcal clinical isolates be determined either by incubation in a high concentration methicillin broth or by disc sensitivity tests which are read only after 48 hours.[12, 59] A recent survey of 322 strains at our own institution using the techniques of Barber has failed to detect resistant strains.[3, 8]

Once present, methicillin-resistant staphylococci have the ability to spread and persist in hospitals. At Boston City Hospital, the first resistant strains were detected in 1967.[5] In the next 12 months, 22

resistant strains were isolated from 18 patients on seven different wards. Four clinical cases on a single ward were believed secondary to contact with a nurse who was a nasopharyngeal carrier.

The virulence of these resistant organisms may be high. A report from France describes a doubling in the mortality of Staph. aureus bacteremia in patients with methicillin-resistant strains.[11] In Denmark during 1966, 10 per cent of all staphylococcal bacteremias were caused by methicillin-resistant strains, but no increase in mortality was observed.[27]

The mechanism of staphylococcal resistance to methicillin is uncertain. Increased production of penicillinase is unlikely, since some resistant strains produce no penicillinase.[17, 55] Prior exposure to the drug does not seem necessary, since resistant strains were detected as early as 1960 in localities in which methicillin had not been used.[28] Other data suggest physical abnormalities in the cell walls of resistant organisms, which may explain the therapeutic failure of methicillin.[12]

The treatment of methicillin-resistant staphylococci is difficult and may require antibiotics of increased toxic potential. Cross-resistance with the other penicillinase-resistant penicillins is usual.[5, 7, 12] In addition, such strains are resistant to penicillin G, cephalothin, erythromycin, chloramphenicol, tetracycline, and kanamycin.[5, 7, 12] In vitro studies suggest synergism between kanamycin and cephalothin or kanamycin and methicillin.[11] Lincomycin, and especially gentamicin, appear potentially useful based upon in vitro observations.[12, 25] Vancomycin has been used with success clinically, but its potential nephrotoxic and ototoxic effects are noteworthy.[7]

Methicillin-resistant staphylococcal infections are obviously important in the individually infected patient. Fortunately, in the overall current epidemiology of staphylococcal disease, they still are of relatively minor importance. Their future significance is uncertain. However, they are apparently widespread, virulent, and communicable. These traits tend to favor their continued spread and increasing importance.

UNTOWARD EFFECTS

In general, methicillin and the other penicillinase-resistant penicillins are relatively nontoxic. The recognized side effects are similar to those occurring with other penicillins and include various skin reactions, reversible granulocytopenia, and a Coombs-positive state.[29, 40, 56, 57] Of special interest are the rare instances of nephropathy.

Renal disease as a manifestation of penicillin hypersensitivity has been known for some time.[15] Typically this was of the "serum sickness" type with the renal pathology characteristically a glomerulitis or vasculitis.[53] In 1961, and many times subsequently, a different type of nephritis was described in patients receiving methicillin.[2, 21] The clinical pattern is characterized by fever, skin eruptions, eosinophilia, proteinuria, hematuria, and sterile pyuria, with varying degrees of azotemia.

The azotemia is usually fully reversible after therapy is discontinued.[2] In one patient, renal impairment progressed to near fatal levels, despite discontinuance of antibiotics 34 days earlier, and then responded to glucocorticoid therapy.[20] Pathologically, infiltration of the renal interstitium with eosinophils, plasma cells, and lymphocytes occurs with accompanying tubular injury. Identical reactions are reported with penicillin G and ampicillin.[20] To date, similar reactions with other penicillinase-resistant antibiotics have not been reported, but most likely this only reflects their more recent therapeutic availability.

Hypersensitivity as the basis of methicillin nephritis is fairly well documented. Methicillin antigen was demonstrated in the renal tubular basement membrane of one patient.[2] Another patient had very high serum concentrations of immunoglobulin G, and electron microscopy demonstrated fibrillar deposits primarily in renal tubular cells.[20]

SUMMARY

Methicillin was the first penicillinase-resistant penicillin clinically available. It is active in vitro and in vivo against the vast majority of staphylococci, pneumococci, and group A streptococci. Methicillin cannot be given orally because of its acid instability. For the same reason, it deteriorates if allowed to stand for several hours in acid intravenous solutions. Methicillin has a low degree of protein-binding, which results in high serum levels of free antibiotic, easy diffusibility into serous cavities, and rapid renal excretion. Accumulation of methicillin in patients with renal insufficiency suggests that dosage should be reduced. Methicillin serum levels are not appreciably influenced by peritoneal dialysis or hemodialysis. Except for differences in dosages and potential routes of administration, there is no experimental or clinical evidence to indicate any significant differences between methicillin and the other semisynthetic penicillinase-resistant penicillins. Methicillin-resistant staphylococci do occur, and may be increasing in incidence, but at present they are only rarely of clinical importance in the United States. Methicillin toxicity is similar to that seen with other penicillins. Of interest are the recent observations of methicillin-induced interstitial nephritis, which is often largely reversible.

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The Isoxazolyl Penicillins: Oxacillin, Cloxacillin, and Dicloxacillin

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The isolation of the penicillin nucleus, 6-amino-penicillanic acid,[7] and its exploitation to modify the penicillin molecule by the addition of a variety of side chains has made feasible the synthesis of penicillins with new and desirable properties.[52] As early as 1960,[38] it was estimated that more than 500 new penicillins had been prepared that could not have been made by fermentation directly. Methicillin, the first penicillinase-resistant penicillin introduced for clinical use, is effective in the treatment of infections caused by penicillin G-resistant staphylococci,[101] but is essentially unabsorbed when given by mouth. The search for more effective orally absorbed penicillinase-resistant penicillins led to the discovery of the isoxazolyl penicillins—oxacillin, and its chlorinated analogues, cloxacillin and dicloxacillin.[28] This review is directed to a discussion of the clinical pharmacology and therapeutic indications of these three antibiotics.

STRUCTURE-ACTIVITY RELATIONSHIPS

Commercial production of oxacillin and its analogues involves the reaction of a synthetically prepared isoxazolyl side chain with 6-

Table 1. *Physicochemical Characteristics of Isoxazolyl Penicillins*

STRUCTURE	ACID STABILITY (activity 2 and 6 hr. at pH 2)	PROTEIN BINDING	URINARY EXCRETION (po/IM)	RENAL CLEARANCE (ml./min./M.²)	HALF-LIFE, MIN. (normal/ anuria)
C—C—[6-APA] oxacillin (N, C, O, CH₃)	85–45%	86–93%	22%/40%	134–169	23/31–48
CL ⟨⟩ C—C—[6-APA] cloxacillin (N, C, O, CH₃)	85–55%	88–96%	21%/33%	95	25/48
CL ⟨⟩ CL C—C—[6-APA] dicloxacillin (N, C, O, CH₃)	93–75%	89–98%	36–75/39–75% †	70	43/62–90
References:	36,77	36,55,75, 90,108,128	5,39,43,50,53, 55,57,59,75, 76,112	92,124	5,10,18,67 92,131

6-APA = 6-amino-penicillanic acid
†Despite variation in urinary excretion, per cent excreted after oral dose equalled that after intramuscular dose in all studies

amino-penicillanic acid nucleus derived from penicillin G (Table 1). The antibacterial activity of the isoxazolyl penicillins, like that of other penicillins, is based on an inhibition of cell wall synthesis through their action as structural analogues of glycopeptide precursors.[121, 132] The phenyl-isoxazolyl side chain is responsible for the penicillinase (betalactamase) resistance of these antibiotics, probably through steric hindrance at the site of attachment of the penicillin and the enzyme. These penicillins are acid stable, permitting oral absorption, and the addition of one (cloxacillin) or two (dicloxacillin) chlorine atoms to oxacillin results in higher serum antibacterial levels and some increased in vitro antistaphylococcal activity (Table 2). Some authors suggest that the increased levels of serum activity are due to a proportional increase in the degree of protein-binding, and decrease in the rate of hepatic inactivation, mediated through the addition of the chlorine atoms.[34, 92] An excellent review of the structure-activity relationships of the penicillins has recently been published by Price, Gourevitch, and Cheney.[82]

ANTIBACTERIAL ACTIVITY

The susceptibility of common bacteria to oxacillin, cloxacillin, and dicloxacillin is shown in Table 2, with the activity of other commercially available penicillins and a cephalosporin provided for comparison.

Table 2. *Susceptibility of Recent Clinical Isolates of Common Bacteria at the Boston City Hospital to a Cephalosporin and Various Penicillins*[50,52][†]

MINIMUM INHIBITORY CONCENTRATION (RANGE / MEDIAN)

GENERIC NAME	Staph. aureus[c]	Staph. aureus§	Strep. group A	Strep. viridans	Entero-coccus	D. pneu-moniae	N. menin-gitidis	N. gonor-rhoeae	Hemophilus influenzae
oxacillin	.1–3.1 / .4	.2–6.3 / 1.6	.02–.4 / .04	.1–3.1 / .2	12.5–>100 / 50	.04–.8 / .1	.1–6.3 / 3.1	.4–12.5 / 3.1	25–100 / 50
cloxacillin	.1–3.1 / .4	.2–1.6 / .8	.02–1 / .04	.1–6.3 / 1.6	25–100 / 100	.1–.8 / .2	.8–12.5 / 6.3	.4–6.3 / 1.6	12.5–>100 / 50
dicloxacillin[‡]	.05–.2 / .1	.05–.8 / .15	.006–.2 / .02	–	50–>100	.01–.1 / .05	–	–	–
methicillin	.4–6.3 / 1.6	.8–6.3 / 3.1	.1–.4 / .2	.1–12.5 / .8	50–>100 / 100	.1–1.6 / .2	.04–1.6 / 1.6	.04–12.5 / 3.1	1.6–25 / 6.3
nafcillin	.2–.8 / .4	.4–.8 / .6	.02–1 / .04	.04–3.1 / .4	12.5–>100 / 25	.02–.2 / .02	.8–6.3 / .8	.2–25 / 3.1	.8–100 / 25
cephalothin	.1–.8 / .4	.1–3.1 / .8	.1–.2 / .1	.02–3.1 /	50	.2–.4 / .2	.1–1.6 / .4	.1–1.6 / .4	3.1–50 / 25
penicillin G	.005–1.6 / .02	3.1–>100 / >100	.002–.2 / .005	.002–.4 / .02	1.6–6.3 / 3.1	.01–.1 / .02	.02–.2 / .1	.005–4 / .04	.4–6.3 / .8
ampicillin	.1–.8 / .2	3.1–>100 / >100	.01–.04 / .02	.04–1.6 / .4	.8–6.3 / 1.6	.01–.04 / .02	.04–.1 / .07	.02–.4 / .2	2.1–16 / .4

†Tests done by inocula replicating method but for dicloxacillin
‡Dicloxacillin data is that of Naumann[75]
Non-penicillinase producers
§Penicillinase producers

Penicillin G is the most effective of these preparations in vitro for all susceptible organisms. The isoxazolyl penicillins are effective at low concentrations against group A streptococci and Diplococcus pneumoniae, though they are less active than penicillin G. Oxacillin, cloxacillin, and dicloxacillin have greater in vitro activity against penicillinase-producing staphylococci when compared with methicillin, but are comparable to nafcillin. None of the penicillinase-resistant penicillins have any significant activity against gram-negative enteric bacilli or enterococci, and have moderate to poor activity against Hemophilus influenzae.

The minimum inhibitory concentrations (MICs) which are listed were obtained using nutrient agar. Determinations performed in pooled human serum have demonstrated a considerable decrease in activity, proportional to the degree of protein-binding for each of the penicillins. The MICs for oxacillin, cloxacillin, and dicloxacillin[1, 59, 90] are 12, 20, and 30 times higher, respectively, in human serum when compared with nutrient broth, while those for benzylpenicillin G (= 60 per cent albumin-bound) are only 2 to 4 times as high. Whether these in vitro results using different media bear any direct relation to in vivo antibacterial activity is by no means certain.

The penicillinase resistance of the isoxazolyl penicillins is not absolute, and all three drugs are slowly hydrolyzed by this enzyme. They are also capable of inducing staphylococci to produce increased amounts of penicillinase. However, there are no indications that inactivation of this group of penicillins by staphylococcal penicillinase is of clinical importance.[29, 36, 77, 82, 112]

Clinical isolates of staphylococci resistant to methicillin and the other penicillinase-resistant penicillins were noted as early as 1960.[18] This resistance appears to be an intrinsic property of the Staph. aureus,[105, 119] probably related to distinct biochemical differences in the bacterial cell wall,[100] independent of the synthesis of penicillinase or drug inactivation. A slow step-wise resistance can be readily produced in the laboratory by repeated transfers of initially sensitive staphylococci through subinhibitory concentrations of these antibiotics.[10] All the penicillinase-resistant penicillins, and in most instances the cephalosporins, exhibit cross resistance with methicillin-resistant strains of Staph. aureus or Staph. epidermidis (Staph. albus).[30, 39, 40, 98, 105, 119] Although the susceptibility of Staph. albus has remained relatively constant,[38] methicillin-resistant strains of Staph. aureus have become of increasing clinical and epidemiologic importance in hospitals, both in Europe and in the United States, within the last few years.[9, 17, 123] In spite of continuous monitoring, no resistant strains of Staph. aureus were found at the Boston City Hospital prior to 1967; in that year the incidence was found to be 1.4 per cent of strains tested.[6] The possibility that widespread use of the penicillinase-resistant penicillins may hasten the emergence of resistant strains[17, 88] should serve to discourage the indiscriminate use of these antibiotics in clinical situations in which therapy with penicillin G would suffice.

ABSORPTION[10, 13, 21, 27, 39, 40, 43, 50, 53-55, 57, 75, 83, 108, 109, 129]

Absorption of orally administered isoxazolyl penicillins occurs primarily in the duodenum and ileum, and may vary widely from dose to dose in the same patient as well as among different patients. Maximum serum levels are attained at 1 to $1^{1/2}$ hours, with persistence of significant activity for 2 to 3 hours after a fasting oral dose. Doubling the dosage provides a proportional increase in peak serum levels and some increase in duration of activity. When taken shortly before or after a meal, delayed gastric emptying and increased acidity interfere with absorption, yielding peak serum levels which are lower and achieved later, although antibacterial activity may persist somewhat longer. The intramuscularly administered preparations of oxacillin and cloxacillin provide serum levels approximately twice those demonstrable with the same amount of drug given as a fasting oral dose. Oral probenecid given with the oral or parenteral isoxazolyl penicillin will result in peak serum antibiotic concentrations almost twice those achieved by the same dose of antibiotic alone, and a prolongation of serum activity.

Cloxacillin provides higher levels of serum antibacterial activity than comparable doses of oxacillin. Dicloxacillin gives levels of serum activity twice as high as cloxacillin and approximately four times higher than oxacillin.

DISTRIBUTION AND PROTEIN-BINDING

After absorption, the isoxazolyl penicillins become attached to hydrophobic receptor sites on the serum albumin molecule.[12] The degree of albumin-binding is thought to depend on the nature of the side chain attached to the penicillin nucleus, and appears to be related to the lipid solubility of this portion of the molecule.[52] Estimates as to the actual percentage of protein-bound, as opposed to free, antibiotic have depended largely upon the techniques used to measure this characteristic (Table 1). It is important to note that, while binding takes place extremely rapidly, this phenomenon is also rapidly and almost completely reversible. An equilibrium therefore exists between the antibiotic-protein complex and free penicillin, not only in the serum, but also in the extracellular fluid and tissues.[87, 125] Thus, although protein-bound penicillin is essentially inactive and relatively nondiffusible between these compartments, it serves as a constant reservoir to replace free antibiotic which has been excreted or destroyed. This complex problem has been the subject of a number of excellent reviews which should be consulted for further information.[11, 56, 59, 90, 128]

Data on the passage of the isoxazolyl penicillins into various body fluids are sparse, and for the most part are based on small numbers of patients treated with these drugs. Insignificant levels of antibacterial activity have been noted following administration of one or several of these isoxazolyl penicillins in the following fluids: normal cerebro-

spinal fluid,[55, 83, 113, 115] aqueous humor of patients with cataracts,[86] ascitic and pericardial fluids,[53] and sweat.[20] Although there are reports of clinical cures of patients with meningitis,[21-97] there are few data on the passage of these penicillins into the cerebrospinal fluid.[113] Significant antibacterial activity has been measured in synovial fluid[55] and pleural fluid[115] following administration of oxacillin and cloxacillin, respectively, under conditions of active inflammation; however, pleural diffusion appears to be quite irregular.[55, 108] Low levels of oxacillin[16] and cloxacillin[102] have been found in the sputum of patients with cystic fibrosis. Oxacillin is excreted into bile[54] and mother's milk.[54] All three isoxazolyl penicillins cross the placental barrier and may appear in cord blood or amniotic fluid.[23, 61, 83]

EXCRETION

While protein-binding and efficiency of absorption are important in explaining the variation in serum concentrations achieved by each of the isoxazolyl penicillins, excretory mechanisms also play a large role in determining these differences.[55, 92] Excretion occurs in part through the kidneys by a combination of glomerular filtration and tubular secretion.[124] The effects of probenecid are due to competitive inhibition of tubular secretion; however, recently other mechanisms have been invoked to explain its mode of action.[71] Both oxacillin and cloxacillin are excreted almost completely unchanged, although separable metabolites with an antibacterial activity equal to that of the parent drug comprise approximately 10 per cent of the urinary levels of both drugs.[77, 89] Excretion by the kidney is extremely rapid[124] with recovery of over 90 per cent of the total amount excreted within the first six hours after administration.

The half-life of the isoxazolyl penicillins in serum is increased only 1½ to 2 times in patients with essentially no renal function,[16, 18, 67, 92, 95, 131] and it has been suggested that extrarenal mechanisms, probably in the liver, also provide major sites of degradation and excretion. Direct measurements in humans and experimental animals have confirmed the biliary excretion of oxacillin[83] and cloxacillin.[77] Studies in uremic patients have shown that the rate of hepatic excretion decreases progressively with the addition of one or two chlorine atoms to the oxacillin molecule.[92]

CLINICAL APPLICATIONS

SOFT TISSUE INFECTIONS.[20, 22, 40, 43, 49, 75, 94, 97, 104, 108, 115, 118, 122, 130] Reports are available on the use of the isoxazolyl penicillins in the treatment of over 500 patients with staphylococcal infections of the skin and subcutaneous tissues. Despite the fact that many of the patients under therapy had serious underlying disease, cure or improvement was achieved in over 85 per cent of cases. The supplemental use of

moist heat, drainage, or surgical debridement was frequently necessary, and may by itself have been sufficient to achieve a cure in many instances; however, studies comparing the responses of patients on antibiotic therapy with patients receiving local treatment alone showed a significantly higher and more rapid rate of improvement in those patients receiving antibiotics.[24, 41] Failure to eradicate the staphylococcus from suppurative soft-tissue foci despite apparent clinical recovery was noted in some cases, and may have been responsible for the 10 per cent incidence of relapses or recurrences which followed therapy with these drugs.[10, 22, 24, 51, 66, 97, 127] Satisfactory results were also obtained in streptococcal cellulitis or abscesses treated with the isoxazolyl penicillins.[49, 104, 122]

LOWER RESPIRATORY TRACT INFECTIONS. Generally favorable results have been reported with the use of oxacillin[17, 94, 97, 127] and cloxacillin[21, 40, 66, 118, 122, 133] in the treatment of over 200 children and adults with staphylococcal infections of the lower respiratory tract. As might be expected, surgical drainage or aspiration was often necessary to achieve a cure when empyema complicated the pneumonia. The persistence of sensitive staphylococci in the sputum despite clinical improvement was noted by a number of investigators.[16, 51, 115] Similarly, the failure of oxacillin to eradicate staphylococci from nasal carriers has also been reported.[1, 106] While the ultimate clinical results were satisfactory in most patients with pneumococcal pneumonia treated with the isoxazolyl penicillins,[20, 21, 122, 130, 133] resolution in some was felt to be unusually slow.[2, 11] Of interest in this regard is the recent isolation of a relatively resistant type 9 pneumococcus with a minimum inhibitory concentration of 6.2 to 10 micrograms per ml. of oxacillin, 12.5 micrograms per ml. of cloxacillin, and 0.39 micrograms per ml. of penicillin.[107] Turck et al. reported the failure of oral cloxacillin in the treatment of two patients with pneumonia due to H. influenzae.[122] Dicloxacillin has also been used with good effect in the treatment of a small number of patients with staphylococcal pneumonia.[43, 75]

BACTEREMIA. There are approximately 100 reported cases of staphylococcal bacteremia treated with oxacillin.[17, 20, 33, 54, 94, 97, 104, 110, 127] About a third of these patients died; the majority of deaths occurred in patients with serious underlying disease, or when identification and drainage of a primary focus was not feasible. The incidence of relapse, despite prolonged therapy at adequate dosage, was particularly frequent in the group with inadequately drained suppurative foci. Cloxacillin[16, 21, 40, 66, 115, 118, 122] and dicloxacillin[75] have been effective in the treatment of a small number of bacteremias due to staphylococci, pneumococci and streptococci. The prophylactic use of oral cloxacillin (250 mg. every 4½ hours for 18 hours) prior to oral surgery failed to prevent a significant bacteremia due to mouth flora in 12 of 52 patients.[126]

BACTERIAL ENDOCARDITIS. Only a few reports of cases of bacterial endocarditis treated with oxacillin or cloxacillin are available. Six cases of probable staphylococcal endocarditis, five due to Staph. aureus and one due to Staph. albus, were cured on prolonged courses of parenteral and oral oxacillin.[17, 51] Nine patients with endocarditis responded

poorly to therapy with oxacillin and cloxacillin; failure was associated with suboptimal dosage,[25] insensitive organisms (enterococci),[33, 115] or prostheses and sutures in the heart.[26, 66, 91] Three of four cases of endocarditis due to Streptococcus mitis were cured with combined oxacillin-streptomycin therapy.[33] Although it has been recommended that oxacillin be given in combination with penicillin and streptomycin as prophylaxis for postoperative infection following open-heart surgery,[3, 68, 78] a limited prospective controlled study could not establish the value of oxacillin prophylaxis.[37]

Osteomyelitis and Septic Arthritis. Therapy with oral or parenteral oxacillin has resulted in a clinical cure in 29 out of 31 infants, children, and adults with acute staphylococcal osteomyelitis.[17, 20, 33, 94, 97, 110, 127] Although immediate results were highly satisfactory, long-term follow-up studies were not available in the majority of patients. Surgical debridement or removal of a prosthetic device was necessary to achieve adequate results in many cases. Reports describing the use of oxacillin in the treatment of chronic staphylococcal osteomyelitis are limited and difficult to evaluate.[14, 20, 97]

Oral cloxacillin has been employed in the treatment of approximately 70 cases of proven or presumed acute hematogenous staphylococcal osteomyelitis.[21, 115, 118] In the largest series reported,[11] 27 patients were treated with a 5 week course of oral cloxacillin, while 35 patients underwent initial bone-drilling in addition to antibiotic therapy. Sequestrectomy or re-exploration was required in four patients in the operative group who ultimately recovered. A single patient, also in the operative group, went on to develop chronic osteomyelitis, providing an absolute failure rate of only 1.9 per cent. Encouraging results have also been reported with the use of cloxacillin in the treatment of chronic staphylococcal osteomyelitis.[8, 16, 21] Initial clinical and bacteriologic cures were achieved in almost all patients; however, the high incidence of relapses associated with apparently healed chronic osteomyelitis suggests that further follow-up studies will be necessary to evaluate adequately the ultimate success of this therapy. Dicloxacillin has been used with success in a single case of acute osteomyelitis of the mandible.[75]

Four cases of staphylococcal[21, 85, 118] and one of pneumococcal[122] arthritis have been cured using irrigation of the joint or systemic therapy with cloxacillin, or both.

Bacterial Meningitis. Clinical and bacteriologic cures were achieved in two patients with Staph. aureus meningitis[97] treated with parenteral oxacillin and one patient with meningitis due to group A beta-hemolytic streptococci treated with oral cloxacillin.[21] Because of concern for the passage of the isoxazolyl penicillins into the cerebrospinal fluid, some investigators have used intrathecal or intraventricular therapy in addition to the systemic antibiotic.[17, 113, 115]

Streptococcal Pharyngitis. Several authors have suggested that dual infection with penicillinase-producing staphylococci may be responsible for treatment failures following penicillin G or penicillin V therapy of streptococcal pharyngitis,[31, 58, 111] pyoderma,[110] or burns.[60] In these instances it was believed that penicillin G was prevented

from eradicating the streptococcus by locally produced penicillinase. Recent studies could not confirm this antagonism,[51, 93] and comparisons of the isoxazolyl penicillins with penicillin G or penicillin V in the treatment of streptococcal pharyngitis have shown generally comparable results.[1, 72, 116, 117] Penicillin G remains the drug of choice in the treatment of streptococcal pharyngitis; the isoxazolyl penicillins may, however, be of value in some treatment failures in which Staph. aureus has been cultured together with streptococci from the pharynx.[69]

MISCELLANEOUS INFECTIONS. In addition to the commonly encountered problems discussed above, the isoxazolyl penicillins have been of value in the treatment of a number of other infections: staphylococcal enterocolitis,[71, 97, 115, 118] peritonitis,[96, 104] ophthalmic infections,[75] pyelonephritis,[97] and miscellaneous dental infections.[45] Recommendations regarding the routine use of oxacillin in the treatment of burns are difficult to evaluate in the absence of control data.[74]

Recent interest has also centered around the use of the penicillinase-resistant penicillins in combination with high doses of benzylpenicillin or ampicillin in the treatment of pseudomonas infections of the urinary tract[39] and chronic bronchitic infections due to H. influenzae.[62] Although the drugs were initially effective in suppressing the infection, a high rate of relapse followed the discontinuation of therapy with these synergistic combinations.

Some investigators have suggested that penicillinase-producing staphylococci in the urethra may interfere with the penicillin therapy of gonorrhea,[73, 104] indicating the need for a drug adequate to deal with both organisms. This bacteriologic antagonism has not been confirmed in a carefully documented study.[51]

TOXICITY AND HYPERSENSITIVITY

The isoxazolyl penicillins are generally well tolerated, but some patients receiving the oral medication may experience gastrointestinal discomfort, with eructations, nausea, and epigastric fullness, particularly when these drugs are given in high doses.[1, 10, 39, 75, 101, 110] These symptoms are rarely severe enough to warrant discontinuation of therapy. Diarrhea, usually beginning 2 to 4 days after onset of oral therapy, also appears to be related to the amount of drug ingested, and, if severe, may necessitate a temporary discontinuance or reduction in dosage.[10, 97] Masking the unpleasant bitter taste of the suspensions with marmalade or a suitable sweetener may be necessary when oral medication is given to children.[64]

Moderate elevations of serum glutamic oxaloacetic transaminase (SGOT), with return to normal levels after discontinuation of therapy, have been reported in some patients following use of the isoxazolyl penicillins.[16, 81, 127, 133] Reversible cholestatic hepatitis has been documented in one patient treated with oral oxacillin.[120] In a patient known to be allergic to penicillin G (angioneurotic edema) and methicillin (pruritus and eosinophilia), abnormalities of liver function, eosinophilia,

and neutropenia developed after $2\frac{1}{2}$ months of continuous oxacillin therapy.[32] Transient leukopenia has also been observed with oxacillin and cloxacillin therapy.[79] Nephropathy of the type associated with methicillin[15] and cephaloridine[114] has not been reported.

Maculopapular, morbilliform, urticarial, or erythematous rashes occur in approximately 3 per cent of patients.[21, 54, 80, 97, 117, 122] Cross-reactions occur among all the penicillins. Although some patients with a history of an immediate penicillin reaction have received oxacillin[19] without ill effect, caution must be used in administering oxacillin, cloxacillin, or dicloxacillin to a patient with a prior history of an allergic reaction to any other penicillin.

Superinfection with gram-negative enteric organisms may be an important complication in some patients receiving oxacillin,[17, 22, 54, 97] cloxacillin,[16, 21, 118, 122] or dicloxacillin.[19] Patients particularly at risk include the elderly, the debilitated, and those with chronic pulmonary infection and ischemic skin lesions. Fungal superinfections have also been described.[54, 115]

In vitro studies with the isoxazolyl penicillins[63, 65] have indicated that oxacillin in high doses may displace bilirubin from its albumin-binding sites. There is concern that the high levels of free bilirubin resulting from this displacement may increase the risk of kernicterus in the newborn; however, this problem has not been observed clinically to date.

ADMINISTRATION AND DOSAGE

The three isoxazolyl penicillins are prepared as capsules and in suspensions for oral administration, but in the United States only oxacillin is available for parenteral use (Table 3). In general, the oral drugs are used for patients with minor infections or to follow a parenteral course when the disease warrants prolonged administration (as in osteomyelitis or endocarditis). Patients with severe infections should be treated initially with the parenteral drug because of the variable absorption of the oral preparations. There is little documented advantage in intravenous as compared with intramuscular administration of oxacillin, but if prolonged therapy is considered, the pain of frequent injections makes the intravenous route advantageous. Food taken at the same time or shortly before the oral isoxazolyl penicillins depresses absorption significantly. A schedule should be advised for the oral preparations to be taken at least 1 hour before or 2 hours following meals. Probenecid may be of value if higher and more sustained levels of serum antibacterial activity are desirable. Administered to adults as one 500 mg. tablet every 6 hours, probenecid should be considered in patients with bacteremia, osteomyelitis, or endocarditis.

The parenteral dose of oxacillin varies between 2 and 12 gm. a day in 4 to 6 doses, depending on the severity of the disease. In the infant and young child, a dosage schedule of 100 to 200 mg. per kg. of body weight of oral or parenteral oxacillin is used. In the newborn

Table 3. *Administration and Dosage Schedules of Isoxazolyl Penicillins*

| GENERIC NAME | TRADE NAME | AVAILABLE FORMS | | | | PARENTERAL DOSE* (gm./day) | ORAL DOSE (gm./day) | APPROXIMATE COST† (10-day course) |
| | | ORAL | | | | | | |
		PARENTERAL	CAPSULES	SUSPENSION				
oxacillin	Prostaphlin Resistopen	250, 500 mg. and 1 gm. vials	250, 500 mg.	250 mg./5 ml.		2-12	2-4	$24-26.00 (500 mg. q.i.d.)
cloxacillin	Tegopen	–	125, 250 mg.	125 mg./5 ml.		–	1-4	$8-12.00 (250 mg. q.i.d.)
dicloxacillin	Veracillin Dynapen Pathocil	–	125, 250 mg.	62.5 mg./5 ml.		–	1-4	$13-16.00 (250 mg. q.i.d.)

*12 gm. of oxacillin contain 27.6 mEq. of sodium
†Prices of capsules obtained from reference 70 and pharmacies in Boston, February 1970

the dosage should be reduced by half and administered in 2 doses per day during the first 2 weeks of life.[22] Approximately half the dosage regimen recommended for oxacillin is used for cloxacillin or dicloxacillin.

For patients in renal failure, modification of the dose and schedule of cloxacillin and dicloxacillin has been recommended,[10, 67, 92, 131] but this does not appear to be critical in such patients receiving oxacillin.[18] Toxicity was not associated with oxacillin in a dosage schedule of 500 mg. every 4 hours given to patients with uremia.[17] Although these penicillins are excreted in part by the liver, no dosage changes are necessary for patients with acute or chronic liver disease.

SUMMARY

Oxacillin and cloxacillin have proven to be safe and highly effective drugs in the treatment of a wide variety of infections due to penicillinase-producing staphylococci. Oxacillin, which is available in parenteral form, should be used in the treatment of severe infections, whereas cloxacillin would be preferred when oral therapy is indicated. Neither of these drugs replaces penicillin G as the drug of choice for infections due to penicillin-sensitive organisms. However, the incidence of penicillin-resistant staphylococcal infections is significant in the patient with community as well as hospital-acquired disease. When the likelihood of a penicillin-resistant staphylococcal infection exists, primary therapy with oxacillin or cloxacillin may be warranted until cultures return, at which time specific therapy can be determined by the antibiotic sensitivity of the infecting organisms. Further clinical experience is needed to evaluate the overall usefulness of dicloxacillin. These drugs should not be used in the patient with a prior history of significant penicillin allergy.

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Ampicillin

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The isolation in 1957 of 6-aminopenicillanic acid from penicillin fermentations[7] led to the production of numerous semisynthetic penicillins, of which ampicillin is the most widely used. Introduced for general use in the United States only 6 years ago, this drug comprised about 20 per cent of the antibiotic drug market during 1969, with sales of approximately $90 million.[58]

CLINICAL PHARMACOLOGY

Ampicillin is the dextro-isomer of alpha-aminobenzylpenicillin.[21] It is active against a number of gram-positive and gram-negative bacteria but is inactivated by penicillinase. It is acid-stable, is not greatly affected by the presence of serum,[65] is only about 24 per cent bound by serum albumin,[50] and is well absorbed orally,[18] regardless of when taken in relation to meals.[47]

Blood Levels and Excretion Following Oral Administration

A single oral dose of 500 mg. in an adult[45, 47] or 25 mg. per kg. in a child[3] yields a peak blood level of 2 to 2.5 micrograms per ml. in about 2 hours, and measurable levels can be detected for approximately 6 hours. With a 1.0 gm. dose these serum levels are doubled. About 25 per cent of the administered oral dose is excreted unchanged in the urine in 12 hours, yielding urine concentrations of approximately 100 to 700 micrograms per ml. following a 500 mg. dose, and 100 to 1450 micrograms per ml. during the first 6 hours after a 1.0 gm. dose.

Blood Levels and Excretion Following Intramuscular Administration

A single intramuscular injection of 500 mg. in an adult results in a peak blood level of approximately 5 to 8 micrograms per ml. in one hour, and minimal activity is still detectable 8 hours later.[17] Doubling the dose doubles the peak blood level. About twice as much drug is recoverable from the urine when the doses are given intramuscularly as when given orally. Probenecid significantly increases and sustains the levels of activity in the serum and decreases the amount of drug in the urine by about 25 per cent.[47]

Largely because of their immature renal function, infants achieve high and prolonged levels of ampicillin. The serum half-life of ampicillin in premature infants during the first week of life is 4.0 hours,[3] compared with 3.4 hours for a term infant during the first day of life.[10] Following a dose of 25 mg. per kg. intramuscularly in infants less than 24 hours old, the level of ampicillin in the serum reaches 55 to 60 micrograms per ml. in one hour and is still 5 to 7 micrograms per ml. after 12 hours. When the infant reaches the age of 4 or 5 days, renal maturation has progressed and the serum half-life of ampicillin decreases from 3.4 to 2.2 hours, with correspondingly lower blood levels.[10] In older children the one-hour peak is about 14 micrograms per ml., and only about 1.1 micrograms per ml. remains in the serum 6 hours after administration.[69]

Blood Levels and Excretion Following Intravenous Administration

Continuous intravenous infusion of ampicillin at a rate of 500 mg. per hour results in blood levels of about 30 micrograms per ml. without probenecid and about 45 micrograms per ml. with probenecid. The renal clearance of the drug is about 75 per cent and is reduced by half when probenecid is used.[86] Although probenecid does diminish the renal tubular secretion of penicillins, this mechanism represents only about 25 per cent of its action in enhancing serum levels of ampicillin. The major factor appears to be a decreased distribution volume in the presence of probenecid, resulting in a larger fraction of ampicillin in the blood.[26]

Influence of Renal Disease on Blood Levels and Excretion

In patients with renal disease, ampicillin administered orally in a dose of 500 mg. every 6 hours yields a serum level of about 32 micrograms per ml. Comparable patients receiving 100 mg. every 8 hours achieve blood levels of about 2.7 micrograms per ml.[51] In patients undergoing peritoneal dialysis with 250 mg. of ampicillin per liter of dialysis fluid, the serum level of ampicillin continues to rise throughout the dialysis, with levels of about 55 micrograms per ml. by the fortieth exchange. In peritoneal dialyses using 50 mg. per liter, the serum concentration of ampicillin levels off after approximately the fifteenth exchange, at about 9.5 micrograms per ml.[51] Depending on biliary excretion and hepatic inactivation of ampicillin, anuric patients show a mean plasma half-life in the range of 8.5 hours.[45]

Distribution in Other Body Fluids

For practical purposes, penicillin G, methicillin, and oxacillin do not penetrate the intact blood-aqueous humor barrier. Below a free plasma level of 21 micrograms per ml., ampicillin does not produce levels in aqueous humor within therapeutic ranges, either, but above this critical plasma level significant intraocular penetration occurs,[66] and probenecid may enhance the levels two to five times.[28]

Ampicillin diffuses readily into the exudate of acute otitis media. In children with this infection, good therapeutic levels can be assayed within 80 minutes after a single intramuscular dose of 250 to 500 mg.[16]

Children with bacterial meningitis in one study[5] were found to have cerebrospinal fluid levels of ampicillin in the range of 1.9 micrograms per ml. one hour after a 25 to 50 mg. per kg. parenteral dose. These levels represented about 11 per cent of the serum level of ampicillin, which was significantly higher than the 4 per cent spinal fluid to serum ratios obtained in patients without evidence of meningeal disease. Another study by the same group 3 years later[82] demonstrated considerably higher cerebrospinal fluid to serum ratios; the mean spinal fluid ampicillin level was 42 per cent of the serum level in one hour, 32 per cent in 72 hours, and 9 per cent 3 days after the beginning of therapy.

Ampicillin levels are high in the gallbladder bile of patients with normal biliary tracts and reach up to 48 times the simultaneous serum levels 4 hours after a single oral dose.[1] In patients with cholelithiasis and cholecystitis but without obstruction, biliary concentrations of ampicillin are lower than in normals but are still quite adequate therapeutically. For example, bile levels of 17 micrograms per ml. (about five times the serum level) are achieved 4 hours after a 500 mg. oral dose,[1] and levels of 13 micrograms per ml. (more than twice the serum level) are reached $1\frac{1}{2}$ to 2 hours after a 500 mg. intramuscular dose.[59] When one gram of ampicillin is given intravenously, drug levels of 57 micrograms per ml. in the bile, 5.5 micrograms per cc. in the cholecystic wall, and 4.7 micrograms per cc. in gallstones have been measured.[18] Patients with obstruction of the cystic duct or of the common bile duct have little or no ampicillin in the gallbladder bile whether the drug is administered orally or parenterally.[4, 59]

Even in the presence of very high blood and urine levels, practically no ampicillin can be detected in prostatic tissue,[93] and, like other non-macrolide antimicrobial agents, the drug does not diffuse through the prostatic epithelium.[92]

Ampicillin readily crosses the placenta and enters the fetal serum and amniotic fluid in significant quantities. When 500 mg. of the drug is given intramuscularly to the mother, peak fetal serum levels of about 2.3 micrograms per ml. are reached in one hour, and amniotic fluid levels are 2.9 micrograms per ml. in 8 hours.[11] Higher concentrations are achieved when the intravenous route is used, and, when 500 mg. are given to the mother, levels are 6.6 micrograms per ml. in the fetal serum in one hour and 5.2 micrograms per ml. in the amniotic fluid in 8 hours. The drug is rapidly eliminated from the fetal serum so that only 1.2 micrograms per ml. remains in 4 hours, but the amniotic fluid levels are

Table 1. *Sensitivity of Bacteria to Ampicillin.*[22, 23, 35, 47, 57, 61, 64, 68, 77, 80, 84, 85, 87, 89]

| ORGANISM | MIC IN MICROGRAMS PER ML. | | FREQUENCY OF RESISTANCE |
	RANGE	MEDIAN	
Staphylococcus			
Non-PCN-ase-producer	0.1 – 0.8	0.2	Never reported
Penicillinase producer	3.1 –> 100.0	> 100.0	Resistant
Diplococcus pneumoniae	0.01– 0.05	0.02	Never reported
Streptococcus			
Group A	0.01– 0.05	0.02	Never reported
Group B	0.04– 0.2	0.1	Never reported
Group G	0.2 – 0.4	0.2	Never reported
viridans	0.04– 1.6	0.4	Never reported
faecalis	0.12– 12.5	1.6	Uncommon (6%)
Listeria monocytogenes	0.08– 0.32	0.16	Never reported
Hemophilus influenzae	0.01– 5.0	0.4	Never reported
Neisseria			
meningitidis	0.01– 0.1	0.04	Never reported
gonorrhoeae	0.02– 0.6	0.2	Never reported
catarrhalis	0.04– 0.12	0.1	Never reported
Salmonella	0.2 –> 100.0	0.8	Rare
Shigella	0.5 – 5.0	0.8	Rare
Brucella	0.25– 0.8	0.4	Never reported
Pasteurella	0.4 – 50.0	0.8	Uncommon
Proteus			
mirabilis	1.0 –> 800.0	3.1	Uncommon (5–10%)
vulgaris	0.5 –> 800.0	50.0	Resistant (35%)
morganii	0.5 –> 800.0	100.0	Resistant (90%)
rettgeri	1.0 –> 800.0	100.0	Resistant (85%)
Escherichia coli	0.8 –> 800.0	5.0	Common (10–20%)
Klebsiella pneumoniae	1.25–> 100.0	> 50.0	Resistant (60–85%)
Enterobacter aerogenes	3.1 –> 100.0	> 100.0	Resistant (60–85%)
Serratia marcescens	100.0 –> 800.0	500.0	Resistant (> 90%)
Herellea vaginicola	25.0 –> 100.0	50.0	Resistant
Clostridium	0.01– 0.05	0.02	Never reported
Bacteroides	0.3 –> 32.0	?	Variable
Pseudomonas	200.0 –> 800.0	> 100.0	Resistant (100%)

sustained, and 1.5 micrograms per ml. is still present 29 hours after initial administration of the drug.[13] The amniotic fluid levels of a living fetus are about five times higher than those of a dead fetus, suggesting active contribution by fetal urinary excretion.

Spectrum of Activity

As shown in Table 1, ampicillin is active in concentrations easily achieved in the serum against a wide range of pathogenic microorganisms.

CLINICAL RESULTS

Middle Ear Infections

Otitis media is characteristically a disease of childhood; the principal bacterial pathogens are pneumococci, group A beta-hemolytic streptococci, and Hemophilus influenzae. Single-drug therapy with oral am-

picillin in 4 doses totaling 50 mg. per kg. per day (maximum 2 gm.) for 7 to 10 days is estimated to be effective in about 80 per cent.[6, 62] This regimen is comparable to therapy with combined oral penicillin and sulfonamide, oral oxytetracycline or oral penicillin used alone, or combined intramuscular penicillin and an oral sulfonamide.[6]

Respiratory Infections

In chronic bronchitis the treatment of acute exacerbations with oral ampicillin in dosage of 250 mg. 4 times daily is approximately equal in efficacy to treatment with the same dose of tetracycline[2] or methacycline[53] or with a single daily dose of doxycycline.[1, 9] Relapse is more frequent with H. influenzae than when D. pneumoniae is the responsible organism. However, reports of occasional clinical isolates of tetracycline-resistant pneumococci[72] and the recent report that some strains of pneumococci have become resistant to erythromycin and lincomycin[46] may be points in favor of using ampicillin as the drug of choice for exacerbations of chronic bronchitis in patients not allergic to penicillins.

Meningitis

In infants less than 2 months old, a large number of organisms, including staphylococci and gram-negative enteric bacteria, are encountered in meningitis. Identification of the specific organism is mandatory to direct therapy, and ampicillin alone is not recommended treatment. Meningeal infection with Listeria monocytogenes, which is seen mostly in neonatal patients and debilitated adults, has been treated successfully with parenteral ampicillin.[52, 61]

Bacterial meningitis in children older than 2 months of age is usually caused by H. influenzae, N. meningitidis, or D. pneumoniae. In view of the prevalence of sulfonamide-resistant meningococci,[20] penicillin G has become the drug of choice for meningococcal as well as pneumococcal infections. For initial therapy, however, the possibility that Hemophilus is present must also be considered, and against this organism ampicillin is as effective as chloramphenicol and therefore represents a logical choice for single-drug therapy. The Los Angeles study conducted from 1963 to 1965 by Mathies et al.[54] compared ampicillin with penicillin or chloramphenicol, or both, in 453 patients 2 months of age or older with meningitis. The patients treated with ampicillin initially received one third of the 24 hour dose intravenously, and then were given 150 mg. per kg. per day, divided into 4-hourly doses, intravenously for at least 2 or 3 days, and then intramuscularly until they were afebrile for 5 days and the spinal fluid approached normal. The clinical course, overall mortality (8.3 per cent with ampicillin), and incidence of neurologic residua (12.5 per cent with ampicillin) were similar in both groups. Fleming and his associates[25] carried out a similar study in 1965 and 1966 on 73 children in Toronto, using a larger dose of intravenous ampicillin, 400 mg. per kg. per day. The high dose was very well tolerated and the clinical results again were good. Because the use of a single drug decreases the incidence of drug reactions and complications, lowers the expense of therapy, simplifies nursing care, and avoids possible antibiotic interference, ampicillin has been generally

recommended for initial treatment of meningitis before the results of laboratory studies are known in children over 2 months of age.

While no strains of Hemophilus influenzae resistant to ampicillin in vitro have been isolated, there is a recent spate of reports describing treatment failures or relapses in patients with Hemophilus meningitis treated with ampicillin. These poor results have been attributed to insufficient concentrations of ampicillin in the spinal fluid,[17, 27, 29] especially following oral administration,[15] or to inadequate access of the drug to focal sequestrations of organisms.[71, 94]

Ampicillin has also been investigated as an agent for prophylaxis of carriers of sulfadiazine-resistant meningococci, and may be superior to oral penicillin G in reducing the carrier state of group B sulfonamide-resistant organisms. Negative nasopharyngeal cultures were achieved in about 70 per cent of carriers during treatment with 500 mg. 3 times a day.[20] It is probable that this dose is necessary to achieve adequate concentrations of the drug in saliva.[19]

Endocarditis

Effective treatment of enterococcal endocarditis is usually achieved with the conventional synergistic combination of the bactericidal agents penicillin G and streptomycin.[40] To avoid the ototoxicity of streptomycin, therapy with ampicillin alone has been suggested as an alternative. About 94 per cent of strains of enterococci are inhibited by concentrations of ampicillin less than 6 micrograms per ml., and ampicillin appears bactericidal at almost the same concentrations at which it is bacteriostatic.[8] Any regimen employing ampicillin alone requires monitoring of serum bactericidal activity. Satisfactory results have been reported with ampicillin in doses of one gram every 4 to 6 hours parenterally for at least 2 weeks and then orally, if the patient is doing well, for another 4 weeks. However, until ampicillin is evaluated further, penicillin G and streptomycin remain the cornerstone of therapy in enterococcal endocarditis. Possibly, the employment of ampicillin with streptomycin or kanamycin will be superior to penicillin G and streptomycin or kanamycin.

Organisms found in gram-negative endocarditis show inconsistent synergism or antagonism when tested against various antibiotic combinations. While recent study of antimicrobial combinations showed synergism between ampicillin and kanamycin against only 30 per cent of the E. coli strains tested, there was no antagonism between these drugs.[60] This combination has been used successfully in treating E. coli endocarditis.[36]

Gonorrhea

Because of the decreasing sensitivity of the gonococcus to penicillin during the past 15 years,[83] newer drugs have been investigated. In separate studies of males with gonorrhea in London[91] and in Atlanta,[56] the success rate following a single oral dose of 500 mg. of ampicillin was approximately 85 per cent. Single doses of 0.75 to 2.0 gm. showed no better results. In more recent studies of American sailors and Filipino

hostesses in Subic Bay, where the prevalence of relatively penicillin-resistant gonococci is even higher than in the United States, 100 per cent of 108 hospitalized women and 99 per cent of 202 men were cured of gonorrhea with a single oral dose of 3.5 gm. of ampicillin given with probenicid.[38]

Gonococcal conjunctivitis progresses so rapidly that immediate treatment with high doses of penicillin G has been recommended. Some workers have advocated the addition of high doses of ampicillin to penicillin G,[76] but it is unlikely that this is necessary.

Intrauterine Infections

The aerobic bacteria most commonly found in pregnant patients following premature rupture of the fetal membranes and prolonged labor are Escherichia coli, Streptococcus faecalis, Streptococcus viridans, and Proteus.[55] Since the minimal inhibitory concentrations of ampicillin for susceptible E. coli and Proteus are commonly in the range of 5 micrograms per ml., oral or intramuscular administration of the drug in 500 mg. doses usually produces inadequate fetal serum levels for effective therapy.[24, 81] Therefore, ampicillin for intrauterine infection should be given intravenously.

A study was conducted in Singapore[75] comparing the response in septic abortion of 50 patients treated with intramuscular penicillin G and streptomycin with 50 patients treated with intravenous and then oral ampicillin. The group treated with ampicillin had fewer complications during therapy and shorter duration of fever than the group of patients treated with a combination of penicillin and streptomycin.

Urinary Tract Infections

In general, ampicillin is effective in treating urinary tract infections due to enterococci, E. coli, or P. mirabilis, and is usually ineffective against infections with Pseudomonas, Klebsiella, or Enterobacter. Acute uncomplicated urinary tract infections almost always are caused by E. coli and respond promptly to treatment with most of the commonly used antimicrobial drugs, including sulfonamides. On the other hand, bacteria isolated from the urine of patients with chronic or recurrent infections tend to be associated with a more resistant flora, and in vitro tests of antimicrobial susceptibility are usually necessary for institution of appropriate therapy. Whether ampicillin offers any distinct advantages as initial therapy in acute uncomplicated urinary tract infections, except, perhaps, in pregnant women where considerations of toxicity to the fetus may preclude the use of sulfonamides or tetracyclines, is doubtful. For example, controlled trials with either a sulfonamide, nitrofurantoin, or ampicillin have failed to demonstrate any difference in the overall effectiveness of these drugs in the treatment of acute symptomatic lower urinary tract infections.[14, 30, 37] Our experience with uncomplicated symptomatic urinary tract infections treated with ampicillin has been uniformly favorable.

However, among patients with asymptomatic bacteriuria, many of whom were known to be *chronically* infected, only 69 per cent of 104

patients treated with ampicillin had sterile urine cultures during therapy. These results were similar to those obtained with several other drugs studied in comparable patients with chronic bacteriuria.[57]

In many of the patients with chronic bacteriuria treated with ampicillin, recurrences frequently were observed within a few days of discontinuing treatment and were due to a relapse with the same bacterial species or strain present prior to therapy. Late recurrences were most often associated with a different bacterial species and were no doubt reinfections. It is important to distinguish between these two distinct types of recurrences because relapses are associated with renal infections more frequently than are re-infections. Our experience in treating patients with relapses indicates that prolonging therapy for 6 weeks is useful in some patients with chronic bacteriuria who relapse after a conventional 1 to 2 weeks' course of treatment.[87]

Although the bactericidal activity of ampicillin may be a theoretical advantage over some of the other drugs in the treatment of deep-seated gram-negative infections, there is little evidence that this is the case. Moreover, it appears likely that among some of the Enterobacteriaceae, at least, the widespread use of ampicillin may result in selection of resistant strains. For example, 96 per cent of 100 consecutive isolates of E. coli studied between 1960 and 1962 were inhibited by 5 micrograms per ml. or less of ampicillin, while only approximately 85 per cent of more recent isolates have been sensitive to that concentration of the drug.

Salmonella Infections

Oral ampicillin was found to be effective in 77 per cent of 40 cases of typhoid fever treated in Egypt, while oral chloramphenicol was effective in all 58 patients treated with this drug.[65] However, when both drugs were administered parenterally in a study in Brazil, ampicillin was just as effective as chloramphenicol.[42] The parenteral dosage of ampicillin recommended is 50 mg. per kg. per day for children and 2 gm. per day or more in 6 hour divided doses for adults. Treatment should be continued for 2 weeks.

About 3 per cent of typhoid fever patients become chronic carriers of Salmonella typhosa and continue to excrete the organisms in the feces for more than a year. Typhoid organisms are usually harbored in the biliary tract, and, when gallstones are present, even prolonged treatment with high doses appears unable to sterilize the center of the stones.[11, 58] Although ampicillin may be superior to chloramphenicol in eliminating the carrier state, Kaye et al.[41] were able to achieve cure in only 50 per cent of 24 patients treated with ampicillin, of whom 17 had gallbladder disease. Simon and Miller were able to eradicate the typhoid carrier state in 13 of 15 patients, 8 of whom had gallbladder disease.[71] Children rarely become Salmonella carriers. For adult carriers the recommended regimen consists of 1.5 gm. of ampicillin in combination with 0.5 gm. of probenecid 4 times a day for 6 weeks. If the cholecystogram is normal, second or third courses of treatment may be successful.[63] Carriers with gallbladder disease who have relapses

after one or more courses of therapy should be considered for cholecystectomy and should be given ampicillin before, during, and immediately after surgery.[74]

Shigella Infections

Shigellosis is usually a mild self-limited diarrheal disease not requiring antimicrobial therapy. In severe cases, the patient should be hospitalized and treated with an antibiotic to which his organism is sensitive. Several studies of therapy for Shigella dysentery have been conducted at the Parkland Memorial Hospital in Dallas, where about 45 per cent of more than 250 pediatric patients admitted each year for diarrhea have shigellosis. When oral ampicillin was compared with sulfadiazine and a placebo in 52 patients, 48 per cent of the strains were susceptible to a sulfonamide and 90 per cent to ampicillin. The bacteriologic failure rate in patients treated with placebo was 75 per cent, with sulfonamide 39 per cent, and with ampicillin only 6 per cent. Clinical failures occurred in 56 per cent of the group given placebo, in 39 per cent of those who took a sulfonamide, and in none of the patients who received ampicillin.[31] When ampicillin was compared with oral neomycin, bacteriologic failures occurred in 87 per cent of the neomycin-treated group, despite apparent susceptibility in vitro, but in only 13 per cent of those treated with ampicillin. Clinical failures occurred in 60 per cent of patients who received neomycin and in 13 per cent of those treated with ampicillin.[31]

When intramuscular ampicillin was compared with oral ampicillin in a dosage of 100 mg. per kg. per day in 4 divided doses, parenteral administration produced somewhat more rapid clearing of Shigellae from the stools and a shorter duration of fever.[32] However, oral therapy was quite effective, even when the dose was lowered to 50 mg. per kg. per day.[33] Patients treated orally with ampicillin were more likely to develop overgrowth of their intestinal flora with Candida, while those treated parenterally tended to have replacement of the normal fecal flora with Klebsiella-Enterobacter species.[32, 33]

Bacteroides Infections

When the infecting organism is Bacteroides, it is difficult to predict the sensitivity to ampicillin. Bornstein and his associates[12] observed that strains isolated from the upper respiratory tract tended to be penicillin-sensitive, and from intra-abdominal and pelvic infections penicillin-resistant, but exceptions were frequent. Nine strains isolated from nonrespiratory clinical specimens in Buffalo[13] showed minimal inhibitory concentrations of ampicillin less than 32 micrograms per ml. and led the authors to conclude that ampicillin is superior to tetracycline against Bacteroides. In contrast, Hoogendijk[39] found minimal inhibitory concentrations of ampicillin greater than 32 micrograms per ml. against 19 of 25 strains of Bacteroides isolated in Amsterdam. He argued that ampicillin has no place in the treatment of infections by these strains and recommended therapy with tetracycline.

Surgical Infections

The comparative safety of ampicillin in patients with leukopenia, hepatic dysfunction, or renal impairment. coupled with its effectiveness against streptococci, pneumococci, gonococci, non-penicillinase producing staphylococci, clostridia, Hemophilus, and most strains of E. coli and P. mirabilis, have prompted its use in a wide variety of surgical infections as the initial therapy before in vitro sensitivity data are available. Rutenberg and Greenburg[70] reported good responses to systemic ampicillin therapy in 19 of 24 patients with wound and soft-tissue infections, in 8 of 10 with lower respiratory infections, in 6 of 11 with intra-abdominal abscesses. but in only 7 of 21 with bacteremia.

TOXICITY, HYPERSENSITIVITY, AND SIDE EFFECTS

Ampicillin shares with benzylpenicillin virtual freedom from toxic effects. Like all penicillin derivatives it is cross-reactive in patients hypersensitive to penicillin G,[78] but there is a lower incidence of immediate anaphylactoid reactions. This difference may be due to traces of a proteinaceous constituent of the fermentation brew detectable in penicillin G and V, and even in 6-aminopenicillinanic acid. but not in the semisynthetic penicillin derivatives.[79]

Delayed reactions, on the other hand. occur frequently with ampicillin. In a recent report of drug surveillance among almost 4000 patients in three Boston hospitals,[73] rashes occurred in 9.5 per cent of patients treated with ampicillin, 4.5 per cent of those treated with other penicillins, and 1.8 per cent of individuals not given these drugs. There was considerable difference among the hospitals. but, in general, rashes occurred during the first week of therapy as often with ampicillin as with the other penicillins, whereas eruptions beginning after the first week were much more common with ampicillin. The incidence of rash with ampicillin appeared not to be affected by its route of administration.

The Boston series included 9 patients with infectious mononucleosis. none of whom received ampicillin and none of whom developed a rash. In a series of 184 patients with this disease in Edinburgh. 19 received ampicillin and 18 of these developed a rash. Although rash is a fairly common finding in infectious mononucleosis. the difference in incidence of rash between the Edinburgh patients not treated with antimicrobials (16 per cent) and those who received ampicillin (95 per cent) is highly significant.[65]

Patients with impaired renal function treated with standard doses of ampicillin develop elevated serum drug levels and an increased incidence of drug rash. In 126 consecutive patients treated with ampicillin studied by Lee and Hill,[51] 28 with renal disease had a 56 per cent rate of untoward reactions while taking 500 mg. of ampicillin by mouth every 6 hours. In contrast, only 6 per cent of 35 patients with normal renal function had untoward reactions with the same regimen. When the dosage for 5 other patients with renal disease was lowered to less than 500 mg. per day, no adverse reactions were observed. The adverse reac-

tions usually consisted of diarrhea or rash and mild fever, but a few patients had severe skin eruptions with desquamation and permanent deterioration in renal function.

COMMENT

Ampicillin is the first of the biosynthetic penicillins to provide increased activity against some of the gram-negative bacteria. It is not penicillinase-resistant and hence is ineffective against penicillinase-producing strains of staphylococci or against gram-negative organisms that produce this enzyme. Actually, ampicillin probably has little more antibacterial activity against many species than is afforded by very high doses of penicillin G. For example, it has been shown that infections with Proteus mirabilis or Escherichia coli may be treated successfully with 10 to 20 million units of penicillin G per day.[10, 90] Comparable antibacterial activity can be achieved with 4 to 6 gm. of ampicillin. Furthermore, the antibacterial spectrum of ampicillin is somewhat similar to the tetracyclines and chloramphenicol. However, its bactericidal property may be a theoretical advantage over these two drugs, particularly in deep-seated infections.

The main role of ampicillin in clinical practice is not entirely clear. Ampicillin appears useful primarily in pediatric medicine. Here, its broad activity against H. influenzae, as well as against D. pneumoniae, group A streptococci, and meningococci, appears to afford a distinct advantage over most other antimicrobials. Its precise role in adult medicine is less certain. To begin with, it is important to point out that the drug should not be used blindly in suspected sepsis, lest the infection be caused by a penicillinase-producing staphylococcus, or by Klebsiella, Enterobacter, or Pseudomonas, which are generally not inhibited by this drug. Secondly, although ampicillin has been effective in the treatment of acute E. coli urinary tract infection, a host of other drugs is also available for this purpose. In addition, ampicillin is much less likely to be effective against other Enterobacteriaceae or Pseudomonas prevalent in chronic bacteriuria, emphasizing that these gram-negative pathogens must be identified and tested for susceptibility in vitro. Thirdly, although ampicillin is employed widely in the treatment of purulent exacerbations of chronic bronchitis, it is doubtful whether ampicillin is superior in this regard to other antimicrobial agents. Fourthly, the variable antibacterial activity of ampicillin against Bacteroides species argues against its use as a sole agent in peritoneal infection.

Finally, as is the case with other penicillins, ampicillin is relatively nontoxic even when given in large doses. However, gastrointestinal distress is quite common when ampicillin is taken by mouth. In addition, because allergic reactions to penicillin have been attributed largely to the degradation products of its 6-aminopenicillanic acid nucleus, it is not surprising that cross-reactions occur with various other mem-

bers of the penicillin family. Although anaphylactic reactions appear less frequent with ampicillin than with penicillin G, rashes appear to be more common.

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The Present Status of Streptomycin in Antimicrobial Therapy

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Streptomycin is less likely to damage the auditory function of the eighth cranial nerve than is dihydrostreptomycin or a combination of the two substances. Dihydrostreptomycin has the property of producing delayed deafness even after administration of the drug has been stopped. Currently, it is recommended that dihydrostreptomycin not be used except in the rare instance in which the patient needs such an agent and can tolerate dihydrostreptomycin but not streptomycin.

In anuric patients, the duration of serum concentrations of streptomycin may be prolonged for 3 to 4 days after a single parenterally administered dose. Consequently, follow-up doses should be given at prolonged intervals, preferably in keeping with determinations of blood levels.

Currently, use of streptomycin is restricted largely to so-called combined therapy, wherein it is given simultaneously with other agents in selected infections because of its possible enhanced antibacterial effect.

Although infections of the bloodstream caused by Streptococcus pyogenes and those due to a streptococcus of the viridans type, such as S. mitis or S. salivarius, may be adequately treated with penicillin G alone, bacteremia due to group D streptococcus (also known as enterococcus), such as S. faecalis, and anaerobic and microaerophilic strains of streptococci, may be managed better by a combined streptomycin-penicillin G or kanamycin-penicillin G therapy or with ampicillin alone (Table 1).

Bacteremia and bacterial endocarditis caused by S. mitis and kindred streptococci have been managed successfully by a regimen of procaine penicillin G plus streptomycin, both injected intramuscularly every 12 hours. More recently, members of our group have been investigating the use of larger doses of penicillin G, given intravenously every 24 hours, with or without smaller daily doses of streptomycin injected

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Table 1. *Use of Streptomycin in Infections Due To Indicated Organisms*

ORGANISM	ANTIMICROBIAL AGENTS		
	FIRST CHOICE	SECOND CHOICE	THIRD CHOICE
Streptococcus viridans (S. mitis, S. salivarius)	Penicillin G or penicillin G plus streptomycin	Erythromycin	Cephalothin, lincomycin, novobiocin, or vancomycin
Enterococcus (Streptococcus faecalis)	Penicillin G plus streptomycin (or kanamycin) or ampicillin, with or without streptomycin (or kanamycin)	Vancomycin	Erythromycin plus streptomycin
Spirillum minus	Penicillin G	Erythromycin	A tetracycline plus streptomycin
Haemophilus influenzae	Ampicillin	Chloramphenicol	A tetracycline plus streptomycin; erythromycin, or sulfonamide
Donovan bodies (of granuloma inguinale)	A tetracycline	A tetracycline plus streptomycin	Chloramphenicol
Salmonella typhosa	Chloramphenicol	Ampicillin	A tetracycline plus streptomycin
Other salmonellae and Arizona organisms	Empiric therapy: a tetracycline plus streptomycin	Empiric therapy: chloramphenicol	Kanamycin; or chloramphenicol; (paromomycin or polymyxin B or colistin by mouth in enteric infection)
	Definitive therapy: ampicillin	Definitive therapy: kanamycin or gentamicin	
Escherichia coli	Empiric therapy: a tetracycline plus streptomycin	Empiric therapy: chloramphenicol plus kanamycin	Polymyxin B or colistin
	Definitive therapy: ampicillin	Definitive therapy: cephalothin	
Klebsiella-Enterobacter-Serratia	Empiric therapy: a tetracycline plus streptomycin	Empiric therapy: chloramphenicol plus kanamycin	Sulfonamides
	Definitive therapy: polymyxin B or colistin	Definitive therapy: cephalothin or gentamicin	
Proteus mirabilis	Empiric therapy: a tetracycline plus streptomycin	Empiric therapy: chloramphenicol plus kanamycin	Cephalothin or novobiocin
	Definitive therapy: penicillin G	Definitive therapy: ampicillin	
Proteus vulgaris, P. morganii, and P. rettgeri	Chloramphenicol plus kanamycin	A tetracycline plus streptomycin	Cephalothin
Achromobacter	A tetracycline plus streptomycin	Chloramphenicol plus kanamycin	Polymyxin B or colistin
Alcaligenes	A tetracycline plus streptomycin	Chloramphenicol plus kanamycin	Polymyxin B or colistin
Pseudomonas	Polymyxin B	Colistin	A tetracycline plus streptomycin or chloramphenicol plus kanamycin

Table 1. *Use of Streptomycin in Infections Due To Indicated Organisms* (Continued)

ORGANISM	ANTIMICROBIAL AGENTS		
	FIRST CHOICE	SECOND CHOICE	THIRD CHOICE
Shigella	Ampicillin	A polymyxin	Gentamicin. kanamycin. paromomycin, or a sulfonamide (by mouth in enteric infections)
Brucella	A tetracycline plus streptomycin	A tetracycline	Erythromycin, novobiocin, or ampicillin
Pasteurella tularensis	Streptomycin	A tetracycline	Chloramphenicol
Pasteurella pestis	Tetracycline plus streptomycin	–	
Listeria monocytogenes	Penicillin G or penicillin G plus streptomycin (?)	A tetracycline or a tetracycline plus streptomycin (?)	Erythromycin
Vibrio comma	A tetracycline plus streptomycin (?)	A tetracycline plus kanamycin (?)	–
Vibrio fetus	A tetracycline plus streptomycin	–	–
Actinobacillus mallei	A tetracycline plus streptomycin	A sulfonamide	–
Malleomyces pseudomallei	A tetracycline plus streptomycin	A sulfonamide	–

every 12 hours, in this type of infection. In enterococcal endocarditis, our group begins therapy with a similar amount of penicillin G plus streptomycin and increases the dosage of penicillin G as required. When the enterococcal bacteremia or endocarditis is refractory, conjoint use of streptomycin and ampicillin may give an enhanced antibacterial effect.

Streptomycin-tetracycline therapy is currently held by many to be the treatment of choice for brucellosis. Streptomycin also has been used in combination with the tetracyclines against serious infections such as bacteremia caused by some gram-negative enteric bacilli, such as Escherichia coli, Klebsiella-Enterobacter, and Proteus organisms, in endarteritis due to Alcaligenes organisms, in pneumonia due to Klebsiella pneumoniae, and in plague. Use of streptomycin against tuberculosis, in combination with other antituberculotic agents, hardly requires reiteration. Tularemia is one of the few diseases in which streptomycin seemingly can be used alone with excellent results; a tetracycline is an effective alternative to streptomycin.

Streptomycin has been used in treating Meniere's disease, and in one report, none of the patients so treated had had a return of symptoms over follow-up periods ranging from 11 to 13 years. Streptomycin did not affect hearing in the normal ear, but hearing of the diseased ear was slightly improved. Results of tests of equilibrium were similar to those obtained in persons with complete loss of vestibular function.[4]

DOSAGE

In adults with normal renal function and of average weight, ototoxic effects are less likely to occur if no more than 2 gm. of streptomycin is administered daily for no longer than 14 days, or 1 gm. is administered daily for as long as 4 weeks.

Although, as aforementioned, infections of the bloodstream caused by S. pyogenes and streptococci of the viridans type, such as S. mitis, may be adequately treated with penicillin G alone, bacteremia due to enterococci such as S. faecalis may be managed better by giving either combined streptomycin-penicillin G or ampicillin.

Bacterial endocarditis caused by S. mitis and kindred streptococci has been managed successfully by means of a 2 week course of procaine penicillin G in doses of 1,000,000 units, plus 1 gm. of streptomycin, both injected intramuscularly every 12 hours.[2] More recently, members of our group have been investigating the use of penicillin G in doses of 20 million units given intravenously every 24 hours, plus 0.5 gm. of streptomycin injected every 12 hours, for 2 weeks in the therapy of this type of endocarditis. We employ a similar regimen in patients with bacteremia due to S. mitis and other viridans streptococci, or give only the penicillin G in amounts of 20 million units or more, but discontinue therapy when the patient has been afebrile for 72 hours and the results of three consecutive blood cultures have been reported as negative.

When a group D streptococcus (enterococcus) such as S. faecalis is the infective agent, aqueous crystalline penicillin G given by continuous intravenous drip and streptomycin injected intramuscularly in amounts of 0.5 gm. every 12 hours have given satisfactory results. We use an isotonic solution of sodium chloride or one containing 5 per cent dextrose in distilled water as the vehicle for the penicillin, and add a small amount of heparin (25 to 50 mg.) to the infusion in the hope that venous thrombosis at the site of insertion of the needle will be delayed. Usually, the rate of flow can be regulated so that half the amount of fluid to be given each day, containing half the daily dose of penicillin, is delivered within 12 hours. The daily dose of penicillin is determined in part by results of the so-called serum bactericidal test; usually the dose varies from 20 to 100 million units. That dosage is accepted when the patient's serum obtained after a given dose of penicillin and diluted 1:8 or more produces an in vitro eradicative effect on cultures of the organisms responsible for the infection. Such a regimen is continued for 4 to 6 weeks in cases of endocarditis,[3] and as described for infections due to S. mitis and related organisms in cases of bacteremia. As aforementioned, ampicillin has given preliminary indications of being as effective as the streptomycin-penicillin G regimen, at least against certain strains of enterococci. Initially, 1 gm. of ampicillin is given parenterally every 4 to 6 hours; after 2 weeks, one considers giving the drug in similar amounts by the oral route. Therapy should be guided by results of serum bactericidal tests and is generally continued for a total of 6 weeks. In refractory cases of enterococcal bacteremia or endocarditis, conjoint use of streptomycin or kanamycin may enhance the anti-enterococcal effect of ampicillin therapy.[1]

UNTOWARD EFFECTS

As noted previously, streptomycin is less likely to damage the auditory function of the eighth cranial nerve than is dihydrostreptomycin or a combination of the two substances. Whereas streptomycin may damage the vestibular function of the eighth cranial nerve, this is not so calamitous as deafness, because the dysequilibrium may be compensated for, at least partially, by ocular mechanisms. Detection of early vestibular and cochlear complications can be effected best if audiometric and vestibular turning tests are done periodically during treatment and again 6 months after its cessation. The incidence of these complications is proportional to the daily dose of streptomycin and to the duration of its administration. The likelihood of ototoxicity is greater in infants, the aged, patients who are dehydrated, and those with impaired renal function. The blood concentration of streptomycin should not exceed 25 micrograms per ml., and the daily dose should be adjusted accordingly.

Whether prior use of streptomycin or of other potentially ototoxic drugs such as kanamycin, neomycin, or vancomycin increases the possibility of an untoward otic reaction on future use of streptomycin is

not known with certainty. However, this possibility should be considered in certain cases when the drug is prescribed. In patients who have suffered ototoxicity on prior use of streptomycin, the use of that agent should be avoided if possible. One should hesitate to give streptomycin conjointly with any other drug that can produce neurotoxic effects, including ototoxic ones.

Possible audiotoxic effects on the fetus caused by transplacental passage of streptomycin should be considered in the treatment of a pregnant woman.

It is especially recommended that not more than 20 mg. of streptomycin per kilogram of body weight be given to infants or young children, because otherwise stupor, flaccidity, coma, and respiratory depression may eventuate. Streptomycin, dihydrostreptomycin, neomycin, kanamycin, polymyxin B, colistin, and, to a lesser extent, the tetracyclines have a potential curariform action that may result in neuromuscular block and consequent respiratory or cardiac arrest. Such an effect is most likely to occur on intraperitoneal or intrapleural administration of these antibiotics and would be most unusual when the drugs are given by other routes. Nevertheless, the possibility should be considered in infants, in the aged, in patients with renal disease or hypoxic states, and in those receiving certain drugs such as muscle relaxants, sedatives, narcotics, and anesthetic agents. Neostigmine, edrophonium, or calcium administered intravenously may counter the reaction. These antibiotics are contraindicated in patients who may have myasthenia gravis.

Mild albuminuria and cylindruria may occur in patients who are receiving streptomycin, but azotemia is rare. In patients with inadequate renal function, azotemia may be accelerated on administration of streptomycin, and if the drug is permitted to accumulate in the blood because of inadequate excretion, ototoxicity may appear earlier. Also, such factors as dehydration and hypotension induced by the infection may augment drug-induced nephrotoxicity or ototoxicity.

During therapy with streptomycin, paresthesia is common but not significant; headache and drug fever are infrequent. A maculopapular rash is the common untoward cutaneous reaction, but exfoliative dermatitis has occurred. Angioneurotic edema is uncommon. Pericarditis is a rare manifestation of allergy to streptomycin and also has occurred after the use of either a penicillin or a tetracycline. Optic neuritis with consequent impairment of vision may follow use of either streptomycin or chloramphenicol, and this possibility is a theoretic reason for avoiding simultaneous use of these drugs;[12] this complication may reflect antibiotic-induced pyridoxine deficiency.

COMMENT AND CONCLUSIONS

When so-called bacteriostatic or suppressive drugs are used, negative follow-up cultures should not cause relaxation of scrutiny, because the infection may recur shortly. Although the terms "bacteriostatic" and "bactericidal" may not be ideal, an understanding of the implications of each term is useful.

With concentrations of drugs unattainable in the body, in vitro agents may demonstrate a killing effect on bacteria, but our group uses the term "bactericidal" to designate drugs that may do so only in vivo. The bactericidal agents include the penicillins, streptomycin, kanamycin, neomycin, gentamycin, bacitracin, polymyxin B, colistin, vancomycin, cephalothin, and possibly lincomycin. Bacteriostatic agents are those whose concentrations in the body are insufficient to kill bacteria, and these produce a reversible inhibition of bacterial proliferation. They may be ineffective when used alone, except in acute, uncomplicated situations. The bacteriostatic agents include the tetracyclines, chloramphenicol, erythromycin, novobiocin, triacetyloleandomycin, sulfonamides, nitrofurans, and nalidixic acid.

However, when a combination of a bactericidal and a bacteriostatic agent is used, it may be bactericidal; this possibility should be determined in the individual infection and preferably verified by so-called serum bactericidal tests. Results of in vitro inhibition tests cannot be accepted without reservation, since a bacteriostatic agent may seem to be indicated on this basis, whereas experience has shown that a bactericidal agent is necessary for effective treatment. Experience also may indicate that certain antibacterial agents will be effective, despite in vitro inhibition tests to the contrary.

Partial bacterial cross-resistance among streptomycin, neomycin, kanamycin, paromomycin, and gentamicin is usual; streptomycin-resistant strains may be sensitive to the other drugs, but organisms insensitive to neomycin, kanamycin, paromomycin, or gentamicin usually resist streptomycin as well.

Empiric therapy often is required in life-threatening infections when the clinical status of the patient makes initiation of treatment necessary prior to the report of microbiologic data. Such empiric therapy is necessary, for example, when a gram-stained specimen of spinal fluid, especially that from a child, reveals gram-negative bacilli. Also therapy may be mandatory when cultures are described as growing a pathogen, yet in vitro bacterial susceptibility tests may not be reportable for another 1 or 2 days. In addition, it is not rare in patients in whom bacteremia due to gram-negative bacilli is strongly suspected clinically for therapy to be initiated empirically after blood is drawn for cultures.[7-9] Therefore, initial therapy cannot be based routinely on the results of cultures and in vitro susceptibility tests, and consequently often is empiric.

There is no dispute regarding the generalization that best results are obtained when the infecting organisms are sensitive on in vitro tests to the antimicrobial agents employed, but the difficulty lies in the unavailability of such data when the clinical status of the patients makes initiation of therapy necessary.

Generally speaking, combined streptomycin-tetracycline or chloramphenicol-kanamycin therapy has been the regimen preferred most frequently by members of our group in the empiric management of serious infections caused by gram-negative bacilli, such as strains of E. coli and Klebsiella-Enterobacter, Proteus, Alcaligenes, and Brucella. Such a regimen, begun before results of in vitro susceptibility

tests were reported in cases in which gram-negative bacillary infection was present or likely, provides broader antibacterial coverage than does a single agent.

Of our patients with serious infection due to gram-negative bacilli in whom such empiric therapy has been employed during the last few years, approximately 70 per cent have received both streptomycin and a tetracycline, and most of the remaining patients have received chloramphenicol and kanamycin. As empiric therapy, a tetracycline has been preferred to chloramphenicol because the latter may depress the marrow, and streptomycin has been chosen over kanamycin because kanamycin is more likely to cause deafness. Currently, our group is investigating colistin (or polymyxin B) along with cephalothin as an empiric regimen in certain of these infections. Other possible empiric regimens that may warrant investigation are cephalothin plus kanamycin or gentamicin, and ampicillin given with kanamycin, gentamicin, colistin, or polymyxin B.

With the advent of newer drugs, we have re-evaluated this policy of the empiric use of combined antibiotic therapy. Colistin, like polymyxin B, has the objection, as an empiric agent, that Proteus and Bacteroides organisms usually are resistant. Kanamycin, if used alone empirically, has the therapeutic inadequacy of not being effective against a number of Pseudomonas and most Bacteroides organisms.

Ampicillin is inactive against Proteus organisms that are indolepositive as well as Klebsiella-Enterobacter and Pseudomonas organisms. Cephalothin is not active against all Enterobacter organisms, Bacteroides, and indole-positive Proteus organisms and usually is inactive against Pseudomonas organisms. Despite in vitro indications of susceptibility, cephalothin may be ineffective against strains of Salmonella, Shigella, and H. influenzae.

Empiric use of combined antibiotic therapy is not without disadvantages. These include the dual depressive effect on the gram-negative elements of the flora and the increased likelihood of superinfection. Like streptomycin and gentamicin, kanamycin is ototoxic but is more likely to cause deafness. Also like streptomycin, the drugs kanamycin, gentamicin, polymyxin B, colistin, and possibly cephalothin are potentially nephrotoxic; except cephalothin, these drugs may cause a curariform effect.

As was aforementioned, chloramphenicol is hematotoxic; and when it is used conjointly with kanamycin, there is also a dual depressive effect on the gram-negative flora. Polymyxin B and colistin can cause cerebellar ataxia and other neurotoxic effects and can induce coccal superinfection. Ampicillin can cause anaphylaxis and the other untoward reactions characteristic of the penicillins, and induces superinfection in about 5 per cent of patients. Cephalothin has caused transient neutropenia and may induce superinfection from Pseudomonas, Enterobacter, and Bacteroides and sometimes other organisms. When the clinical course of the patient is satisfactory, usually the empiric regimen is continued despite in vitro susceptibility tests that indicate bacterial resistance. If renal function is impaired, the dose of

these drugs is correspondingly reduced. Periodic study of the sputum and the stools during therapy may reveal floral changes and impending superinfection.

When the patient is not doing well clinically, the empiric regimen is replaced with the following agents in keeping with the results of the susceptibility tests. Ampicillin, polymyxin B, or colistin may be useful in infections due to E. coli; like kanamycin, gentamicin, and chloramphenicol, those drugs inhibit the organism in vitro in 80 per cent or more of cases; except for ampicillin, the same drugs are considered against Klebsiella-Enterobacter organisms. Cephalothin inhibits Escherichia organisms in about 70 per cent of cases. Streptomycin and the tetracyclines inhibit E. coli in about 50 per cent of cases. Cephalothin, kanamycin, polymyxin B, colistin, and gentamicin inhibit Klebsiella organisms in at least 70 per cent of cases, but in only 20 to 30 per cent of these cases is there susceptibility to streptomycin. Enterobacter organisms are susceptible only to polymyxin B, colistin, kanamycin, or gentamicin. The susceptibility of Serratia bacilli is virtually restricted to kanamycin and gentamicin. Some workers avoid the use of polymyxin B and colistin when possible in non-pseudomonal infections because the drugs may produce relatively low serum and tissue levels.

Among other drugs, ampicillin, penicillin G, novobiocin, cephalothin, kanamycin, and gentamicin are active against the indole-negative P. mirabilis, which causes 80 to 90 per cent of clinical infections due to Proteus organisms. Kanamycin, chloramphenicol, and cephalothin may be applicable to infections caused by indole-positive Proteus organisms (P. vulgaris, P. morganii, and P. rettgeri). As a single agent, kanamycin may be the drug of choice against indole-positive Proteus organisms, because dichotomies between in vitro and in vivo results using chloramphenicol are common, and cephalothin is applicable in only 10 to 20 per cent of cases. Streptomycin or kanamycin given conjointly with chloramphenicol or cephalothin may have an enhanced effect against these bacilli.

Edwardsiella organisms may be susceptible to several antibiotics, including the tetracyclines, chloramphenicol, kanamycin, gentamicin, and ampicillin.

Polymyxin B, colistin, or gentamicin is the drug of choice against Pseudomonas.

Ampicillin, kanamycin, gentamicin, a tetracycline, or chloramphenicol may be applicable to Salmonella or Arizona infections.

Strains of Shigella may resist the action of the sulfonamides in as many as 80 per cent of cases, and chloramphenicol and the tetracyclines may be resisted in 15 to 40 per cent. Consequently, such drugs as ampicillin[s] and kanamycin may be preferable in systemic infection. In enteric shigellosis, these drugs and others such as polymyxin B and colistin can be given by the oral route.

In Citrobacter bacteremia, polymyxin B, colistin, kanamycin, gentamicin, a tetracycline, or chloramphenicol usually is indicated on in vitro studies.

Streptomycin has little or no application in infections due to Bacteroides or H. influenzae.

A tetracycline combined with streptomycin is preferred by members of our group in the management of brucellosis,[5, 10] but some workers prefer only a tetracycline given for longer periods.

Of the infections due to Pasteurella organisms, plague probably is best treated with combined use of streptomycin and a tetracycline. Tularemia responds to either streptomycin or a tetracycline. In infections due to P. multocida (P. septica), penicillin G is the drug of choice, although erythromycin or a tetracycline may be an effective alternative.

In treatment of polymicrobic infections, several drugs may be given simultaneously: for example, penicillin G and streptomycin in enterococcal infection, and simultaneously a tetracycline to combat Bacteroides organisms. Because it is difficult to know which organism is most important in polymicrobic infections, the physician gives broad coverage. However, one attempts to keep the number of agents minimal and rarely resorts to such an antibiotic umbrella. In selected polymicrobic infections, ampicillin and cephalothin may have special application.

"Cure" is determined only by the patient's progress from both the clinical and laboratory points of view after the cessation of therapy.

Careful analysis of individual infections and the use of common sense in therapy are urged; there is no place for diagnostic or therapeutic dogma in the management of infections due to streptomycin-susceptible microbes.

Superinfections[6] may reflect one of the following mechanisms: (1) in a patient with a mixed infection, too few resistant bacteria may be present to be isolated regularly on culture, but the resistant strains become dominant with treatment and eradication of susceptible organisms; (2) in a patient who is receiving an antimicrobial agent that is influencing the growth of the normal body flora, overgrowth of those organisms unsusceptible to the drug may occur because their natural bacterial antagonists have been eliminated, and these endogenous bacteria may spread to the lungs, urinary tract, blood, and other sites normally unavailable to them (occurring during penicillin therapy); and (3) in a patient whose susceptibility to infection is reduced by other diseases or whose flora has been disturbed mechanically or by antimicrobial therapy, exogenous organisms may spread from the environment or from persons therein and take up determined habitat (staphylococcal enterocolitis).

Superinfections are manifested clinically and microbiologically by the appearance of new symptoms and findings, or by the reappearance of those recently eliminated, in a patient at a time when the initial process appears to be responding to a given antimicrobial regimen. Such superimposed or secondary infections may appear at the original site of infection or at sites unassociated with the original process. The intestinal tract, respiratory tree, urinary tract, and bloodstream may be sites of superinfection.

The phenomenon of superinfection due to antibiotic-induced changes in the bacterial flora may be noted as early as the fourth or fifth day after initiation of therapy. Cessation of therapy responsible for a change in the bacterial flora is usually followed by return to a normal

flora within days, but in certain patients with disease characterized by lowered general resistance, such may not occur for several weeks.

In addition to enterocolitis, staphylococcal pneumonia or bacteremia may be a manifestation of exogenous or endogenous superinfection. In endogenous superinfection, the bacterial flora are most likely to be influenced toward superinfection by such drugs as streptomycin, the tetracyclines, the sulfonamides, chloramphenicol, kanamycin, and neomycin, which may eliminate the Enterobacteriaceae, the natural bacterial antagonists of staphylococci.

In a sense, the opposite situation may occur in relation to the penicillins, erythromycin, novobiocin, and allied agents, which depress the coccal members of the body flora and encourage the production of bacteremia, urinary infection, or pneumonia by E. coli and allied organisms. By periodic examination of the sputum and stools, one may be able to detect antimicrobial-induced changes in the body flora in time to avert the development of clinical superinfection.

In general, subjects most susceptible to superinfection are infants, persons with pulmonary disease, patients with a defect in immunizing capacity, and those receiving a tetracycline or combined antimicrobial therapy.

Strains of staphylococci, yeast, and Proteus and Pseudomonas organisms seem to be the most commonly encountered ones in systemic or visceral superinfections.

The significance of yeasts appearing in the oropharynx and intestines during treatment with antimicrobial agents is often obscure and may not result in a clinically identifiable syndrome. Rarely, however, serious complications may ensue, and diffuse infection with involvement of the meninges, heart valves, and other organs may result in death.[11]

Therapeutic failures in infections may depend on (1) lack of clear indications for instituting therapy with streptomycin, (2) poor selection of the drug in the individual case, (3) futile attempts at prophylaxis, (4) failure to appreciate the necessity for surgical drainage or removal of necrotic nidi, (5) superinfection, re-infection, or metastatic infection, (6) underlying disease that may make recovery impossible, (7) toxic or allergic reaction, (8) premature discontinuation of therapy, (9) failure to observe the patient after apparent control of infection, and (10) failure to realize that other investigative and therapeutic procedures are indicated if response to an appropriate antibacterial regimen is poor.

From the statistics on the total consumption of streptomycin and the known incidence of infectious diseases susceptible to its action, it is evident that the drug often is used when it is not required.

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The Tetracyclines

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It has now been over two decades since the introduction of the tetracyclines, the third major antibiotic to become available after penicillin and streptomycin. Since the initial isolation of chlortetracycline from Streptomyces aureofaciens by Duggar in 1948,[9] there has been a continued search for active chemical variants in fermentation products and by chemical alterations of the basic molecule. This has resulted in the development of a number of analogues in the laboratory.

Table 1 lists seven major analogues of tetracycline. Six of these are now on the market in the United States. Oxytetracycline was produced by Streptomyces rimosus and was introduced in 1950. Tetracycline was introduced in 1953 after being prepared by catalytic hydrogenation of the chlorine radical. Demethylchlortetracycline, produced by a mutant of Duggar's original strain, was described in 1957 and became available for clinical use in 1959. Methacycline and doxycycline have become available during the past 3 years. Minocycline was first announced at the Interscience Conference on Antimicrobial Agents and Chemotherapy in October 1966. It is still in the investigational stage, but its properties are somewhat different; therefore, it is of interest.

The structural relationships of the seven tetracycline analogues are shown in Figure 1.[1, 10] The differences are all in positions five, six, and seven of the basic naphthacene ring system. A number of other homologues have been developed in the laboratory but have not yet gained wide acceptance.

CLINICAL PHARMACOLOGY OF TETRACYCLINES[31, 40, 42]

The tetracyclines are incompletely absorbed from the gastrointestinal tract; large though variable amounts can be recovered from the stools after oral administration. They are absorbed by the stomach, duodenum, and ileum, but very little is absorbed by the colon. The amount that can be recovered from the stools varies with different analogues and in different individuals. This property may contribute to

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Table 1. *Tetracyclines*

GENERIC NAME	YEAR INTRODUCED	TRADE OR BRAND NAME	HALF-LIFE (HOURS)	USUAL CAPSULE DOSE (MG.)	USUAL INTERVAL BETWEEN DOSES	USUAL TOTAL DAILY DOSE
Tetracycline hydrochloride	1953	Achromycin Kesso-Tetra Rexamycin Steclin Sumycin Tetrachel Tetracyn Panmycin	8.5	250	6 hours	1-2 grams
Tetracycline phosphate complex		Tetrex		250 500	6 hours 12 hours	1-2 grams
Chlortetracycline	1948	Aureomycin	5.6	250	6 hours	1-2 grams
Oxytetracycline	1950	Terramycin	9.6	250	6 hours	1-2 grams
Demethylchlortetracycline	1957	Declomycin	12	150 300	6 hours 12 hours	300-1200 mg.
Methacycline		Rondomycin	14	150 300	6 hours 12 hours	600 mg.
Doxycycline hyclate		Vibramycin hyclate	20	50 100	12-24 hours	200 mg. first day; 100 mg. daily after first day
Minocycline	1966	Not commercially available				
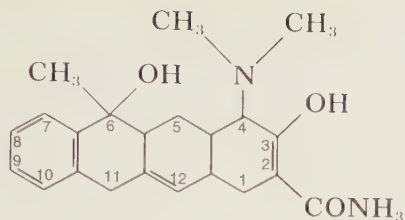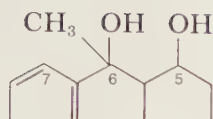
Tetracycline

Oxytetracycline
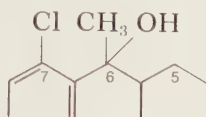
Chlortetracycline
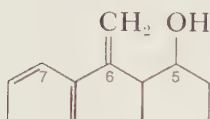
Methacycline
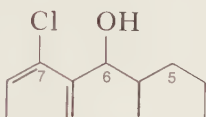
Demethylchlortetracycline
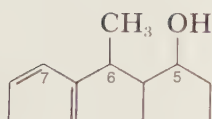
Doxycycline
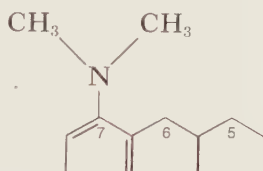
Minocycline

Figure 1.   Structural relationship of tetracycline analogues.

changes in fecal flora and anal irritation. Absorption is increased, and higher blood levels are attained if the antibiotic is taken during the fasting state. Doxycycline absorption appears to be less affected by food than does that of other analogues. Gastric irritation is diminished if the drug is taken after meals, especially when larger doses are being administered.

The tetracyclines are inactivated by the formation of chelates when they combine with metallic ions, chiefly calcium and magnesium,[15] in the gastrointestinal tract. Hence, the absorption of oral tetracycline is impaired when the drug is taken with milk products or with other drugs

containing calcium, magnesium, or aluminum. Aluminum hydroxide markedly reduces absorption.

The tetracyclines diffuse well into most body fluids and tissues. They are present in the milk of lactating women and pass through the placenta into the fetus. They appear in the saliva, cornea, sclera, iris, and vitreous humor. Levels are lower in the spinal fluid than in the blood and vary somewhat with different analogues, as well as from individual to individual. Tetracyclines diffuse into ischemic tissue in measurable amounts.[38]

The greatest difference between analogues has been demonstrated in the duration and concentration of blood levels. Steigbigel, Reed, and Finland have published a careful study of the absorption and excretion of five tetracycline analogues in normal young men.[10] Their observations show that a single 300 mg. dose of minocycline yields the highest and most prolonged blood levels. A single 500 mg. dose of tetracycline hydrochloride yielded blood levels at 2, 4, 8, and 24 hours of 2.88, 3.25, 1.97, and 0.53 micrograms per ml. of serum respectively. No detectable blood levels were obtained at 48 hours. Following a single dose of 300 mg. of demethylchlortetracycline, blood levels of 0.97, 1.74, 1.68, 0.53, and 0.17 micrograms per ml. of serum were obtained at 2, 4, 8, 24, and 48 hours respectively, demonstrating somewhat more prolonged blood levels but no higher than those obtained with tetracycline hydrochloride. A single 300 mg. dose of minocycline yielded blood levels of 9.01, 8.30, 7.04, 3.03, and 1.55 micrograms per ml. of serum at the same time intervals. These values were calculated as "tetracycline equivalents." The blood levels for doxycycline and methacycline were similar to each other. They were higher than those for tetracycline and demethylchlortetracycline hydrochloride but lower than those of minocycline. All but tetracycline yielded detectable blood levels at 48 hours, although the levels at 48 hours were quite low. When given in recommended doses, all of the tetracyclines give adequate blood levels for most organisms that are sensitive to tetracycline therapy.

The principle mechanism of excretion is by way of the kidneys, probably by simple glomerular filtration.[22] The highest concentrations in the urine are produced by tetracycline hydrochloride and the lowest by minocycline. Thus it is evident that the analogue with the most prolonged blood levels has the lowest renal excretion rate, while the other analogues are intermediate. The excretion rates for several homologues have been studied under various conditions of pH, urine flow, and renal function by Kunin and associates.[21, 22] Others have confirmed their studies. The half-life of tetracycline plasma levels is prolonged in the presence of oliguria and renal failure. For example, the half-life of tetracycline plasma levels may increase from a normal value of 8 hours up to 108 hours in some patients with renal failure. Chlortetracycline is an exception, since it is rapidly inactivated in alkaline solutions at body temperature; its half-life is not significantly affected by renal failure.[22] Data regarding minocycline, doxycycline, and methacycline in the presence of renal failure are sparse, but since the half-life of these homologues is longer than that of tetracycline, oxytetracycline, and

chlortetracycline, one should be even more cautious in using these homologues in the presence of impaired renal function and in pregnancy. Tetracycline crosses the peritoneal membrane slowly in patients with renal failure while they are undergoing peritoneal dialysis.[16]

Data on the fecal excretion of tetracyclines are limited, but individual variations among analogues are marked.[10, 12] This may in part account for variations in the amount of tetracycline recovered in the urine.

The tetracyclines are bound to plasma protein in varying amounts. The difference in protein binding may influence the levels obtained in spinal fluid and various other body fluids. The exact significance of protein binding is not clear since it is reversible. It may be an important factor affecting the difference in renal clearance rate among various analogues.

The tetracyclines are concentrated in the bile and the liver. They have an affinity for fast-growing tissues, liver, tumors, and areas of new bone formation. When observed under ultraviolet light, some tetracycline compounds exhibit fluorescence. This property has been explored as a test for various malignancies, including gastric carcinoma, carcinoma of the kidney, and pleural effusions. Malignant cells that have been stained with tetracycline may exhibit fluorescence when examined microscopically under ultraviolet light. These tests have not been widely adopted for routine use.

THE CLINICAL ANTIMICROBIAL SPECTRUM OF TETRACYCLINES[14, 39]

Table 2 outlines most of the important diseases and organisms that are usually responsive to tetracyclines and divides infections into three groups. Group I consists of those that are almost always sensitive to tetracyclines. Tetracycline is either the antibiotic of choice or virtually equal in effectiveness to the antibiotic that is usually considered first choice.

Group II consists of those organisms for which tetracyclines are not the treatment of choice, but they are usually effective and can be used when the first choice drug cannot be used.

Group III includes infections and organisms which may be sensitive to tetracyclines, but treatment with tetracycline is usually not effective, or much more effective therapy is now available.

In general, no important differences have been documented in the clinical effectiveness of tetracycline analogues, despite differences in duration and concentration of blood levels. With the exception of minocycline and staphylococci, a given organism will be resistant to all analogues if it is resistant to one. Individual strain differences in susceptibility of different organisms to the different analogues have been demonstrated by Steigbigel, Reed, and Finland.[39] Their studies showed that minocycline is the most active of the seven analogues against all of the coccal organisms that were tested except enterococci and against most of the important gram-negative bacilli except Proteus. Demethyl-

Table 2. *The Clinical Antimicrobial Spectrum of the Tetracyclines*

I. TREATMENT OF FIRST CHOICE	II. NOT TREATMENT OF FIRST CHOICE BUT USUALLY EFFECTIVE	III. TREATMENT INEFFECTIVE OR MORE EFFECTIVE THERAPY IS AVAILABLE
Diplococcus pneumoniae (if patient is allergic to penicillin)	Diplococcus pneumonia	Endocarditis
Pasteurella tularensis	Streptococcus hemolyticus, Group A (sensitive strains)	Staphylococcal infections, especially bacteremia
Brucellosis	Streptococcus, Group B (sensitive strains)	Gram-negative bacillary bacteremias
Pseudomonas pseudomallei (melliodosis)	Anaerobic streptococci (most strains)	Meningitis
Vibrio cholera (cholera)	Listeria monocytogenes	Chronic osteomyelitis
Bacterioides	Bacillus anthracis (anthrax)	Empyema and suppurative pericarditis
Mycoplasma pneumoniae	Erysipelothrix insidiosa	Septic arthritis
Rickettsial infections including:	E. coli (some strains)	Tuberculosis
Rocky mountain spotted fever	Hemophilus influenza	Leptospirosis
Typhus fever, murine	Neisseria gonorrhoeae	
Epidemic typhus	Shigella	
Rickettsial pox	Hemophilus Ducrey – chancroid	
Q fever	Pasteurella pestis (plague) combined with streptomycin	
Relapsing fever (Borrelia novyi and Borrelia recurrentis)	Malleomyces mallei (glanders)	
Psittacosis	Mima-Herellea (some strains)	
Lymphogranuloma venerum – granuloma inguinale (Donovanosis)	Clostridia tetani	
Inclusion conjunctivitis	Clostridia welchii	
Actinomycosis	Treponema pallidum (syphilis)	

chlortetracycline was most active against Proteus. However, the tetracyclines are not generally considered as first choice in treatment of Proteus, and this observation is of limited practical value. Infections due to the following organisms almost always respond well to the tetracyclines except as indicated:

Pasteurella infections, including multicida, tularensis, and pestis, are all very responsive to tetracycline therapy. Some authors consider streptomycin as the antibiotic of first choice and tetracycline second choice, although they appear to be of equal efficacy.[32]

Brucella infections respond to 0.5 gm. tetracycline four times daily for 3 weeks. Relapse is treated by re-treatment with the same dose. Some authorities recommend 2 weeks of streptomycin, 0.5 mg. intramuscularly twice daily, in combination with tetracycline therapy for more seriously ill patients. There is little evidence that the combination is superior to tetracycline alone.

Cholera. Tetracycline, 500 mg. every 6 hours for the first 48 hours, has been uniformly effective in reducing the duration and volume of diarrhea and in eradicating Vibrio from the stools. Replacement of fluid and electrolyte losses is equally or more important.

Bacterioides infections. Almost all strains are inhibited by 3 micrograms per ml. of tetracycline or less, but abscess formation is so common in bacterioides infection that response is usually not dramatic until abscess cavities are drained surgically.

Mycoplasma pneumoniae infections are almost uniformly sensitive to tetracycline therapy and respond to doses of 500 mg. four times daily. Therapy should be continued for 2 weeks to prevent relapse.

Rickettsial infections of all types are uniformly sensitive to tetracyclines, especially when therapy is instituted early in the course. Recommended therapy is 25 mg. per kg. as an initial loading dose, followed by 25 mg. per kg. daily in divided doses every 6 to 8 hours. Therapy is continued until 48 hours after the patient becomes afebrile.

Relapsing fever due to *Borrelia novyi* and *Borrelia recurrentis* responds dramatically to 2 gm. tetracycline per day for 7 to 10 days.

Psittacosis responds consistently to 2 to 3 gm. per day of tetracycline. To avoid relapse, therapy should be continued for at least 7 days after defervescence. Improvement usually begins within 24 to 48 hours after starting therapy.

Inclusion conjunctivitis, lymphogranuloma venereum, and actinomycosis all respond well to tetracycline therapy.

Infections due to the following organisms are frequently responsive to tetracycline therapy, but other antibiotics are considered first choice:

Diplococcus pneumoniae. Almost all strains are uniformly sensitive to all of the tetracyclines. There have been 20 cases of tetracycline-resistant pneumococcal pneumonia reported in the world literature.[14, 36, 45] Whether this will be a problem of increasing magnitude is not yet clear. Penicillin is the antibiotic of choice in pneumococcal infection.

Group A beta hemolytic streptococci. Between 50 and 60 per cent of strains are sensitive to 1.6 micrograms per ml. There are minor differ-

ences in sensitivity between the various homologues, although mino-
cycline was more active than the other tetracyclines.[39] However, from
20 to 40 per cent of group A beta hemolytic streptococci are insensitive
to tetracycline, and penicillin is considered to be first choice.[14, 20] Tetra-
cycline would be acceptable only after culture and sensitivity test
demonstrated sensitivity.

Anaerobic streptococci are generally sensitive and respond to
tetracyclines as well as to penicillin. Infections with these organisms
require prolonged therapy until abscesses have been drained and
necrotic tissue has been debrided.

Listeria monocytogenes is usually sensitive to tetracyclines, ampi-
cillin, and penicillin. Ampicillin is the drug of choice.

Gonococcal infections have been shown to respond to tetracycline,
demethylchlortetracycline, and doxycycline.[14, 20, 15] Although penicillin
is considered to be the treatment of choice, almost equally good results
are obtained from tetracycline therapy. So-called nonspecific urethritis
responds well to tetracycline when treated for 1 week or longer.

Syphilis. Tetracycline in doses of 2 gm. per day for 2 weeks is an
effective second choice antibiotic for syphilis when penicillin is contra-
indicated.

Clostridium tetani and welchii. Although penicillin is the anti-
biotic of choice in these infections, tetracycline inhibits these organisms
and penetrates ischemic tissue. However, antibiotic therapy is secondary
in importance to adequate debridement and in the case of tetanus, early
adequate doses of antitoxin. There has been at least one report of tetra-
cycline-resistant clostridial infection.[18]

TREATMENT OF CLINICAL ENTITIES AND SYNDROMES

Chronic Bronchitis and Bronchiectasis[29]

There have been a number of studies documenting the efficacy of
long-term tetracycline therapy in these conditions. Therapy may be
either continuous or intermittent for a period of years. Such therapy
usually results in reduction in quantity of sputum and decrease in
purulent character of the sputum. There is a reduction in febrile epi-
sodes and improvement in sense of well being. The author has followed
several patients with both chronic bronchitis and bronchiectasis, usually
on a continuous regimen of 500 mg. to 1 gm. per day, for several years.
No adverse effects have been observed, although such patients should
be followed with periodic blood counts, determinations of BUN, and
occasional liver function tests.

It is generally considered that tetracycline therapy exerts a favor-
able effect by reducing infections due to the pneumococcus and He-
mophilus influenza, but it seems probable that the beneficial effects have
a broader basis than these two organisms alone.

Chronic Bacilluria and Recurrent Urinary Tract Infections

While the practice of prolonged "prophylactic treatment" with
tetracycline therapy is fairly widespread, there is little documentation

that this is effective or desirable, particularly when indwelling catheters, renal stones, or other predisposing factors are present. Gram-negative organisms are particularly prone to be replaced by organisms that are resistant to tetracyclines after prolonged or repeated use.

Acne

Long-term low-dosage tetracycline therapy is widely used in the treatment of acne vulgaris. The usual dose is 250 to 500 mg. per day for periods of months to years. There is good documentation that such therapy exerts a favorable effect on the course of the disease.[7] Tetracycline is excreted in the sebum by binding of the antibiotic to cells and egress via desquamation or sebum excretion, resulting in reduction in the number and frequency of the skin lesions.[12] There is little evidence of toxicity or adverse side effects of such doses in these patients.

Prophylactic Therapy

Prophylactic therapy with tetracyclines has no established place in any infection unless one considers its use in chronic bronchitis and bronchiectasis. The author would consider this as treatment instead of prophylaxis since it is usually employed only after purulent sputum is already being produced.

SIDE EFFECTS AND TOXICITY OF TETRACYCLINE

Table 3 tabulates the most important side effects and toxicities associated with tetracycline therapy. Most of these are self-explanatory, but the following comments will amplify some of them.

Allergic reactions are relatively infrequent, but bona fide allergic reactions have been documented, including rash, urticaria, angioneurotic edema, and a few deaths from anaphylactic reactions.[2, 11, 33]

Gastrointestinal side effects are among the most frequent, especially nausea and diarrhea.[10, 13]

Hepatic toxicity deserves special comment.[8, 30] Abnormal liver function tests, including elevation of SGOT, SGPT, and alkaline phosphatase, as well as increased thymol turbidity and BSP retention, have been observed during administration of tetracyclines. Fatty metamorphosis has been demonstrated histologically. A small but significant number of hepatic deaths have been attributed to tetracycline administration.[30, 37, 43, 50] These have nearly all occurred in women during the latter part of pregnancy while they were being treated with large doses intravenously. Most had severe infections and shock. Postmortem examinations revealed extensive fatty infiltration of the liver but no necrosis. It appears that the combination of pregnancy, sepsis, shock, and large doses of tetracycline renders the liver vulnerable to lethal toxicity. Jaundice has been an ominous sign in such cases. It is now recommended that such patients not be given more than 1 gm. of tetracycline per 24 hours. Probably other antibiotics should be used as first choice in pregnant women with shock and sepsis.

Skin. Tetracycline is concentrated in the skin, and some patients

Table 3. *Side Effects of Tetracycline*

Allergic	Rash, urticaria, anaphylactic reaction
	Angioneurotic edema
	Simulated lupus erythematosus
Gastrointestinal	Glossitis, stomatitis
	Cheilosis
	Nausea, vomiting
	Diarrhea, proctitis
Hepatic toxicity	Abnormal liver function tests
	Fatty metamorphosis
	Lethal hepatic toxicity — especially when associated with pregnancy, shock, and sepsis
Skin	Phototoxicity, onycholysis, rash
Renal	Azotemia
	Fanconi syndrome (due to degraded outdated tetracycline)
	Nephrogenic diabetes insipidus — demethylchlortetracycline
Metabolic	Catabolic effect
	Azotemia
Hematologic	Anemia, neutropenia, eosinophilia — rare
Teeth	Staining, dysgenesis, fluorescence (due to administration of tetracycline during last half of pregnancy and first 5 years of life)
Miscellaneous	Bulging fontanelle — meningeal irritation
	Increased intracranial pressure
Superimposed infections	Monilia
	Gram-negative infections and resistant strains
	Staphylococcal infections

develop hypersensitivity to sunlight with development of marked erythema and bullae. This has been observed somewhat more frequently in southern climates in the summer, where sunlight is more intense. Demethylchlortetracycline has been most frequently responsible, although any tetracycline may provoke this reaction. Degraded outdated tetracycline has been responsible for a syndrome simulating systemic lupus erythematosus.

Renal. Three separate effects have been described.

1. Fanconi syndrome.[6, 25] Several cases have been observed due to the administration of outdated degraded tetracycline. These have been reported by several different investigators. Proteinuria, glycosuria, acidosis, aminoaciduria, weakness, lethargy, hypokalemia, and phosphaturia were clinical features.

2. Nephrogenic diabetes insipidus due to demethylchlortetracycline has been observed in three cases.[5, 14] The effect was reversible 4 weeks after the drug was discontinued.

3. Azotemia[34, 35] during tetracycline therapy has been attributed to interference with protein synthesis by tetracycline and decrease in utilization of amino acids, resulting in an increased load of amino acid metabolites being presented to the kidney for excretion. There is no

concomitant rise in creatinine, and a specific renal lesion has not been demonstrated. The azotemia is reversible after tetracycline is discontinued.

Hematologic effects. Anemia, neutropenia, and eosinophilia have been observed but have rarely constituted a problem.

Teeth.[3, 24] Staining, dysgenesis, and fluorescence of affected teeth have been observed in a large percentage of children when tetracycline was administered to their mothers during the last half of pregnancy and to them during the first 5 years of life. Discoloration occurs when the tetracyclines are given during the formative period of the crowns of the teeth. For the deciduous teeth, this is from midpregnancy to about 4 to 6 months postnatally, and for the permanent anterior teeth, from 6 months to about 5 years of age.

Miscellaneous. Bulging fontanelle due to increased intracranial pressure in infants and meningeal irritation with papilledema in adults has been observed.[17] It is apparently benign and is reversible when the drug is withdrawn.

Superimposed infections may be a problem, especially in patients who have received multiple antibiotics, who are debilitated, or who are receiving immunosuppressive drugs or steroids. Monilial infections, resistant gram-negative bacilli, and staphylococci are the most common superinfecting organisms.

PREPARATIONS AND ADMINISTRATION

Table 1 lists the most common commercially available tetracycline preparations, the trade or brand names, and the commonly available capsule size and recommended dose. In addition, rolitetracycline (Syntetrin) is commercially available for parenteral use only.

The dosages and frequency of administration of the various tetracyclines vary with rate of excretion, protein binding, and half-life. At recommended dosages and frequency of administration, the different tetracyclines are comparable in clinical effectiveness. The slower rates of excretion and the longer half-lives of demethylchlortetracycline (12 hours), methacycline (15 hours), and doxycycline (20 hours) compared to tetracycline (9 hours) permit a reduction in dosage and in frequency of administration of these tetracyclines.[23]

Since the tetracyclines are excreted almost entirely by the kidneys, the long-acting tetracyclines should not be used in the presence of renal failure. Doses should be less frequent when renal function is impaired.

The absorption of all oral tetracycline preparations is impaired when they are taken along with milk products, food or drugs that contain calcium, magnesium, or aluminum.

Parenteral administration should be employed when the infection is severe, when the patient is vomiting or unable to take oral medication. Because of the danger of hepatic toxicity, intravenous tetracyclines should not be administered in a dose of more than 2 gm. the first day and no more than 1 gm. per 24 hours thereafter. If there is renal impairment or oliguria, the dose should be further reduced. Generally, tetracyclines

should be avoided during pregnancy except in exceptional circumstances because of the likelihood of dental staining in the fetus and potential hepatic toxicity to the mother.

Although there are some individual strain differences in sensitivity, this is of little practical importance.

It is less expensive for the patient if a prescription is written with the generic name, tetracycline hydrochloride, than if a brand or trade name is used. No other tetracyclines are available by generic name except tetracycline hydrochloride. Some of the newer tetracyclines have the advantage of being administered in the fewest doses per day. This may be an advantage for the ambulatory patient who is working.

Liquid preparations are available for most of the analogues. These are useful for pediatric use and some adults who have difficulty swallowing capsules.

While there are some preparations that can be administered intramuscularly, most of these contain lidocaine or procaine to minimize pain, but persistent tenderness prevents prolonged administrations by this route. If the individual dose does not exceed 100 mg., the drug is better tolerated, but the blood levels achieved are lower than those that can be obtained when the drug is given orally or intravenously.

There are preparations available for topical application, such as ophthalmic and otic solutions and ointments. These are effective in superficial infections, but for severe infections, systemic therapy is more reliable. Troches and surgical powders containing tetracyclines have been available for many years, but data to document their efficacy appear to be sparse.

Despite the side effects and limitations described in this paper, the tetracyclines remain one of the most useful and one of the safest of all antibiotics. Undoubtedly, many lives have been saved by their administration. The judicious observation of the principles set forth here may contribute to the more specific use of the tetracyclines.

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The Clinical Use of Chloramphenicol

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Chloramphenicol was isolated from *Streptomyces venezuelae* in 1947[21] and was shown to inhibit a wide range of microorganisms.[69] In spite of its remarkable therapeutic effectiveness, controversies exist regarding its indicated use because of infrequent but severe hematologic side effects and the discovery of newer effective antimicrobial agents. These new effective drugs have reduced the practical usefulness of chloramphenicol. Yet, there are clinical circumstances when chloramphenicol is warranted and preferred.

Chemistry and Mechanisms of Action

The chemical structure[5, 51] of chloramphenicol has been confirmed by synthesis[16] (Fig. 1). It consists of: (A) a propanediol moiety, (B) a dichloracetamide side chain, and a (C) p-nitrophenyl group. Of the four possible stereoisomers, only the D(−) threo isomer is active.[63] Protein synthesis is inhibited by the compound apparently at the ribosome by preventing the condensation of amino acids and short chain peptides to polypeptide chains.[45, 72, 73, 103, 104, 108, 113] Subtle but distinct differences have been noted in the action upon mammalian as compared to microbial cells.[4, 8] Other mechanisms of inhibition of protein synthesis and of amino acid transport have been demonstrated.[12, 28, 39, 51] The interference with antibody synthesis has been noted.[2, 11, 19]
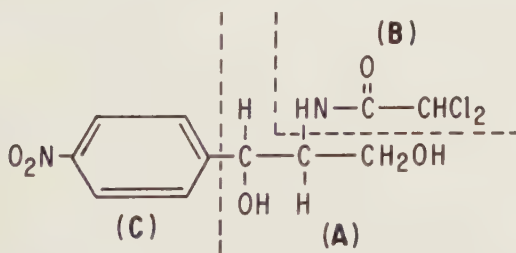
Figure 1. Chloramphenicol.

Availability and Dosage

Chloramphenicol U.S.P. is available in capsules containing 50, 100, or 250 mg. for oral administration. The succinate ester of chloramphenicol for intravenous use is packaged in vials containing the equivalent of 1.0 gm. of active drug. A palatable oral suspension of chloramphenicol palmitate containing 125 mg. of the active base in each 4 ml. of suspension is used for children. Each of these esters is inactive until hydrolyzed after administration. Succinate ester given intramuscularly results in lower and delayed blood levels of active drug than those attained with oral or intravenous administration.[20]

The antibiotic is also available in various solutions, ointments and creams for ophthalmic, otic, and topical use.

The usual dosage of chloramphenicol is 50 mg. per kg. per day divided into four doses at 6 hour intervals for adults and children. Premature and newborn infants and patients with impairment of hepatic and renal function require less than this amount to achieve therapeutic levels. During the early stages of very severe or life-threatening infections, the drug may be given at twice the recommended dosage; i.e., 100 mg. per kg. per day. The dosage should be reduced as soon as possible. Also, higher doses are advised when moderately resistant organisms are encountered; i.e., MIC – 15 to 50 micrograms per ml. The oral route is preferred, when feasible, since the drug is readily absorbed. The contents of the powdered capsules may be suspended in a suitable fluid medium and given by gastric intubation. In those patients unable to take oral medication the succinate ester may be given intravenously as a 10 per cent solution; it is given slowly over at least one minute, or incorporated in intravenous fluids such as isotonic saline or 5 per cent dextrose. Oral therapy should be substituted as soon as practical. Chloramphenicol palmitate is slowly hydrolyzed to the active drug by pancreatic lipases in the duodenum, with release of free chloramphenicol which is then absorbed. Therefore, blood levels with palmitate are slightly lower and are achieved more slowly than with chloramphenicol capsules.

The treatment of premature infants, children in the first few days of life, and those with impaired hepatic and renal function should be approached carefully. Inability of the liver to metabolize and excrete chloramphenicol may result in excessive blood levels of active drug. Monitoring of drug levels by microbiologic testing is not ordinarily available; hence, doses should not exceed 25 mg. per kg. per day, and consideration should be given to increasing the interval between doses in patients in whom the half-life of the drug may be increased.[37, 109, 117]

Pharmacologic Aspects

Chloramphenicol is rapidly absorbed from the gastrointestinal tract.[29, 49, 58, 86, 88] After a single 1.0 gm. oral dose, peak levels are obtained in 2 to 4 hours and approximate 10 micrograms per ml. or more. Sustained administration every 6 to 8 hours provides an accumulated effect with somewhat higher peak levels. The drug readily diffuses into extravascular fluids, such as cerebrospinal fluid, bile, pleural fluid, ascitic fluid, saliva, vitreous and aqueous humors, and milk. Levels

reach approximately one-third to one-half the blood concentrations.[1, 6, 29, 36, 49, 55, 88, 112]

The drug readily crosses the placental barrier. Its use in pregnancy should be restricted at term or during labor, since the fetal liver is unable to detoxify the antibiotic.[87, 92]

Chloramphenicol is inactivated by liver enzymes, mainly by conjugation with glucuronic acid, although other inactive compounds are formed. The inactive conjugates and the active drug are readily excreted by the kidney. Comparisons of levels determined by the colorimetric (active and conjugated chloramphenicol) and the microbiologic (active drug) assays reveal that 75 to 90 per cent of the drug is excreted in the inactive form. However, the relative rapid clearance of the drug gives urine concentrations of unaltered chloramphenicol which exceed 200 micrograms per ml.[58, 86]

In Vitro Activity[22, 24, 69]

Chloramphenicol inhibits a broad range of microorganisms, including most gram-positive and gram-negative bacteria, as well as Rickettsias, Chlamydia (psittacosis-lymphogranuloma viruses), and Mycoplasmas. Its effect is mainly bacteriostatic. Groups of organisms that are notably resistant are the pathogenic fungi and the Pseudomonas and Achromobacter species. Other gram-negative bacteria are usually very sensitive to the action of chloramphenicol, but individual isolates may be resistant. The prevalence of resistance varies from time to time in geographic areas and hospitals. Episomal R transfer factors frequently may impart resistance from one strain to another.[26, 46, 98, 107] Except for the aforementioned groups and genera, the majority of gram-negative organisms are sensitive. The use of antibiotic sensitivity tests are most helpful guides for the clinician.

Adverse Reactions

The following warning accompanies all preparations of chloramphenicol except those used topically. Physicians should be alert to possible adverse effects.

WARNING

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective, as described in the "Indications" section. *It must not be used in the treatment of trivial infections where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.*

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

BLOOD DYSCRASIAS.[7, 9, 17, 18, 23, 25, 27, 34, 43, 47, 50, 57, 60, 68, 74, 75, 89, 91, 105, 114] Two types of bone marrow depression are associated with chloramphenicol usage. The first, a dose-related anemia, is characterized by a reticulo-cytopenia, and perhaps a leukopenia, cytoplasmic vacuolization of early erythroid cells, increase in serum iron and iron binding capacity, reduced uptake of ^{59}Fe by the red cell, and increases in bone marrow cellularity and in the ratio of myeloid to erythroid elements. These changes are progressive but regress promptly upon withdrawal of the drug. Close hematologic surveillance is therefore recommended.

Fortunately, the second type of hematologic aberration is infrequently encountered. A usually irreversible pancytopenia may occur after administration of chloramphenicol. This aplastic anemia does not seem to be dose related and may occur weeks or months after therapy has been discontinued. No satisfactory explanation for this bone marrow depression has been shown, although various mechanisms have been postulated.[14] The risk is difficult to measure accurately because of the concomitant use of other drugs, the inability to establish denomi-nators of chloramphenicol usage, and the difficulty in establishing the risks of aplastic anemia unassociated with chloramphenicol. A study in California estimated that the risk was 1:25,000 or less.[106] Thrombocytopenia, leukopenia, neutropenia, and paroxysmal nocturnal hemoglobinuria have been reported but are less well documented than reversible bone marrow depression and aplastic anemia.

The effect of phenylalanine in reversing the vacuolization of eryth-rocyte precursors in the phenylketonuric infant has led to its use during or after chloramphenicol therapy to prevent or reverse vacuoliza-tion.[31, 42, 93, 110] Benefit from the administration of phenylalanine to prevent or cure aplastic anemia is questionable, and it is debatable whether reversible anemia can be affected by the use of this amino acid.

GRAY BABY SYNDROME.[10, 52, 61, 71, 80, 101, 109] In premature and newborn infants aged 2 weeks or less, the immaturity of hepatic and renal metabolic functions results in higher tissue and blood concentrations in relation to doses of chloramphenicol administered. High doses of chloramphenicol, of 100 mg. per kg. or more, given to many such infants for 3 or more days has produced a rapidly progressive and fatal syndrome. The heralding symptoms are abdominal distension, with or without vomiting, and poor feeding. This is followed in 12 to 24 hours by vaso-motor collapse, with abnormally low temperatures, shallow irregular respirations, and a peculiar ashen cyanosis. Death occurs shortly there-after.

The severity of this syndrome is related to the height of free drug levels which are related to the dosage. The defect may result from inhibition of protein synthesis with accompanying increase in plasma amino acids and ammonia with autointoxication due to hyperamino-acidemia.

Except in unusual circumstances, the administration of chloram-phenicol to premature infants or full-term infants in the first 2 weeks of life is not recommended. If a life-threatening infection caused by an agent susceptible only to chloramphenicol exists, the daily dose of

the drug in these infants should not exceed 25 mg. per kg. unless anti-biotic levels are determined.

OTHER ADVERSE REACTIONS. As with most antibiotics, other less serious untoward reactions have been encountered with chloramphenicol. Some of these reactions are attributable to derangements in normal flora, and include gastrointestinal manifestations of nausea, vomiting, diarrhea, enteritis, glossitis, stomatitis, and pruritus ani. Other side effects are the hypersensitivity reactions of drug fever, rashes, angioedema, anaphylaxis, and Herxheimer-like responses.

Unusual neurologic sequelae resulting from long-term therapy are optic, retrobulbar, and peripheral neuritis, headache, depression, and mental confusion. These are rare. Children and young adults with cystic fibrosis generally constitute this group receiving long-term therapy.[15, 40, 44, 48]

Often, serious complications associated with chloramphenicol have occurred in patients whose illness did not warrant its use. Serious morbidity and mortality from this and other antibiotics are often avoid-able when the highest standards of medical practice are applied.

Clinical Efficacy

It is well known that chloramphenicol is highly therapeutically effective in a great variety of clinical infections. However, a rare but recognized incidence of serious side effects attributable to the drug have alerted the physician to restrict its use to certain reasonably defined categories.

1. INFECTIONS IN WHICH CHLORAMPHENICOL IS SUPERIOR TO OTHER DRUGS OR THE DRUG OF CHOICE. *Typhoid fever and other salmonelloses.* The effectiveness of chloramphenicol for treatment of acute typhoid fever was demonstrated in 1948, and has been fully substantiated. Other drugs show in vitro activity against the typhoid bacillus but are clinically ineffective. Ampicillin has shown significant therapeutic benefit in patients with enteric fever. Yet, critical studies have demonstrated that ampicillin is uniformly less effective than chloramphenicol in arresting the acute symptoms of typhoid fever.[62, 85, 99] It is our opinion that chloramphenicol is the drug of choice. Ampicillin is more effective when given parenterally than when given by mouth. It is clearly the drug of choice in typhoid carriers.[94]

In salmonelloses other than acute salmonella gastroenteritis (septicemia, meningitis, cholecystitis, osteomyelitis, and localized abscesses) chloramphenicol has been uniformly less effective. Dramatic responses and therapeutic ineffectiveness vary between patients and causative strains of salmonellae. Ampicillin may be therapeutically beneficial in such salmonella infections, and like chloramphenicol its effect is not always predictable.

Rickettsial diseases. The first therapeutic triumph for chloramphenicol was the cure of patients with epidemic typhus fever.[79] Soon patients with scrub typhus, murine typhus, and Rocky Mountain spotted fever were cured dramatically with cloramphenicol.[59, 82, 95, 97] The tetracycline antibiotics were subsequently shown to be equally effective in these rickettsioses; the physician has a choice based on his therapeutic judgment. Patients with Q-fever respond to chloramphenicol or

the tetracyclines. A few sparse reports suggest that chloramphenicol is more effective in patients with Q-fever hepatitis.[81]

Melioidosis, tularemia, and plague. Melioidosis is an acute septicemic illness which may end fatally in a few weeks or occur as a milder disease which is localized and self-limiting. It was initially recognized in Malaysia, but isolated infections have occurred in Central and South America and in the United States. Clinically, it may resemble severe infections caused by Pseudomonas aeruginosa. Chloramphenicol is very effective in melioidosis and some investigators consider it the drug of choice.[78]

Streptomycin clearly is the drug of choice for treatment of tularemia or plague. It is bactericidal and very effective, but must be administered parenterally. In the laboratory, bacterial resistance of Francisella tularensis and Pasteurella pestis has been reported; this has not been shown under natural conditions. Under circumstances of epidemic proportions, or the occurrence of antibiotic resistance to streptomycin, chloramphenicol or the tetracycline antibiotics can be relied upon to cure patients with tularemia or plague. Although bacteriostatic in their action, they will effectively ameliorate the acute clinical manifestations.[66, 67, 70, 76, 96]

Eye infections. Chloramphenicol excells in the treatment of eye infections because of its broad gram-positive and gram-negative spectrum and the ability of topically applied solutions to penetrate into ocular tissue.[1, 53, 54] A sterile stabile preparation is now available and overcomes the disadvantage of adding diluent to sterile powder prior to use.[3]

Pulmonary infections. Psittacosis, tularemia, and Q-fever may be characterized by acute pneumonitis; these infections do not respond to penicillin or its analogues. Each of these types of pneumonitis is characterized by normal or low blood leukocyte counts. Streptomycin is very effective in tularemia. Chloramphenicol and the tetracyclines are effective in each of these less common types of pneumonias, some of which may be fatal.

2. Clinical Infections from Which the Etiologic Agent Has Been Isolated and Shown to be Sensitive Only to Chloramphenicol. Occasionally, infections are encountered in which the offending pathogen is inhibited only by chloramphenicol. With the introduction of semisynthetic penicillins, cephalosporins, kanamycin, gentamicin, and other antibiotics, isolation of organisms sensitive only to chloramphenicol is less frequent.

Certain strains of the genus Bacteroides, for example, are sensitive *only* to chloramphenicol.[30] These investigators found chloramphenicol to be clinically effective and considered it the drug of choice. In these serious clinical circumstances, the clinician should exercise his clinical judgment in spite of the remote possibility of serious blood dyscrasia.

3. Serious Infections When the Etiologic Agent Has Not Been Isolated and Chloramphenicol Provides the Broadest Antimicrobial Coverage. Physicians are often faced with the necessity and obligation to institute therapy in a potentially life-threatening infection based on clinical evidence when confirmatory laboratory data is neither

helpful nor available. He must make a therapeutic decision based on the calculated clinical possibilities. An antibacterial spectrum of action is desired which will provide therapeutic benefit over a broad range of etiologic possibilities.

Bacterial meningitis is a prime example of this clinically common threat. The effectiveness of chloramphenicol far outweighs the minimal risks of deleterious side effects.[38, 77, 111]

There are circumstances, in individual patients, when the seriousness of the infectious process and inadequate knowledge of etiology or antibiotic sensitivity predicates the use of chloramphenicol in the therapeutic regimen. One of its prime attributes is prompt infusion into the cerebrospinal fluid in high concentration when given intravenously.

Ampicillin is very effective in the pyogenic types of bacterial meningitis. There are reports of failure with ampicillin in the treatment of Hemophilus influenzae meningitis.[13, 32, 35, 56, 90, 116] Host hypersensitivity often precludes use of ampicillin or penicillin G, the drug of first choice in pneumococcal and meningococcal meningitis.

4. CLINICAL INFECTIONS IN WHICH THE PHYSIOLOGIC STATUS OF THE PATIENT PRECLUDES USE OF OTHER ANTIBIOTICS TO WHICH THE ORGANISM IS SENSITIVE. Hypersensitivity of the patient to penicillin or its analogues places chloramphenicol as an important *alternate* microbial drug. Pyogenic meningitis caused by Diplococcus pneumoniae, Neisseria intracellularis, and H. influenzae are examples of this clinical situation. Chloramphenicol approximates penicillin or ampicillin in efficacy in these serious bacterial types of meningitis.[64, 65] The physician has, with chloramphenicol, an antibiotic which cures patients with these serious types of meningitis. It is not the drug of choice but an important form of alternative therapy.

Added to this broad therapeutic range of antibacterial activity is the isolated good effect of chloramphenicol in patients with meningitis caused by Listeria, Salmonella, Klebsiella, etc.[33, 83, 100, 102] These and other findings emphasize its therapeutic capability when needed for patients with meningitis.

Acute toxic manifestations due to excessive blood levels of some antibiotics in patients with renal failure often creates therapeutic problems. If such drugs are to be given, serum or urine concentrations must be determined in relation to dosage and renal function. Chloramphenicol is not nephrotoxic, is eliminated readily by the diseased kidney, and may be given to patients in renal failure with relative impunity.

In patients with sickle cell disease and obvious sepsis, chloramphenicol is often indicated in view of the high incidence of superimposed salmonella infections. The decision to use chloramphenicol in any of the specific categories mentioned, or in combination with other agents, rests upon the judicious appraisal of the therapeutic alternatives and an estimation of the attendant risks.

When this careful evaluation indicates that chloramphenicol is the best drug and offers immediate therapeutic and obvious clinical advantage over other alternatives, it should be used. Fear of rare or late hematopoietic abnormalities should not deter its use. Its use without these judicious guidelines is ill-advised. Chloramphenicol should not be used

for minor infections, for ordinary chemoprophylaxis, or for long-term therapy.

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Erythromycin

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Erythromycin is an antibiotic produced by an actinomycete, Streptomyces erythreus, originally isolated from a soil sample obtained from the city of Ilo-Ilo on the island of Panay in the Philippine Archipelago. The antibiotic was first produced, purified, used clinically and reported in 1952 by McGuire and his associates.[71] Five detailed reviews are now available.[21, 22, 26, 33, 44] The spectrum of antimicrobial activity of erythromycin includes those organisms commonly encountered in clinical practice. After more than 15 years of experience in the treatment of bacterial infections, erythromycin has achieved an enviable record with regard to therapeutic effectiveness and safety.

CHEMISTRY

Erythromycin is one of a group of antibiotics with a macrocyclic lactone nucleus, called a macrolide.[71] Of the six macrolide antibiotics that have been made available commercially, erythromycin, oleandomycin, and tylosin (agricultural use only) are available in the United States.

Wiley[108] reported the structural formula of erythromycin. The propionyl ester of erythromycin was developed by Stephens and was further modified by preparation of its lauryl sulfate salt.[97] The complete formula for erythromycin and its derivatives is shown in Figure 1. The generic name, propionyl erythromycin lauryl sulfate, was changed to erythromycin estolate by the U.S.P. Erythromycin is basic (pK_a = 8.6), as compared with propionyl erythromycin, which has a pK_a of 6.9.[97] Studies on the mechanism of drug absorption by Schanker et al.[91] have shown that organic compounds are probably absorbed in the un-ionized

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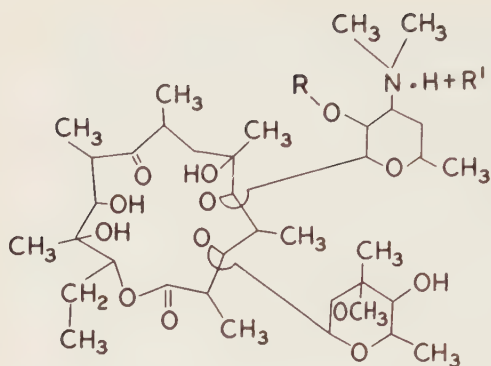
Figure 1. Structural formula of erythromycin.

	R	R¹
Erythromycin	H	
Propionyl erythromycin	CH_3CH_2CO	
Erythromycin estolate	CH_3CH_2CO	$C_{12}H_{25}OSO_3$
Erythromycin stearate	H	$C_{17}H_{35}COO$
Erythromycin ethyl succinate	$CH_2CH_3OOCCH_2CH_2COO$	

form; therefore, the pK_a of a substance has a bearing on its ionization and absorption in the intestinal tract. This may explain why the propionyl ester with a pK_a of 6.9 has greater absorption than other erythromycin derivatives when administered orally.[97]

The base, the stearate salt, the propionyl ester, and erythromycin ethyl succinate are relatively insoluble in water but readily soluble in organic solvents such as acetone or methyl or ethyl alcohol. All of these derivatives are susceptible to acid inactivation while in solution. Acid degradation may be reduced by making relatively insoluble salts of the base or by protecting the base with a special enteric coating.[97]

Two relatively water-soluble salts of erythromycin, gluceptate, and lactobionate, are available for intravenous injection. A formulation using the ethyl succinate ester is also available for intramuscular injection.

BACTERIOLOGY

The antibacterial spectrum of erythromycin is more extensive than that of penicillin G. It is most effective in vitro against gram-positive cocci, such as Staphylococcus aureus (both penicillin-sensitive and penicillin-resistant), beta-hemolytic streptococci and Streptococcus viridans, enterococci, and pneumococci. Neisseria meningitidis and gonorrhoeae and some strains of Hemophilus influenzae, pasteurella, brucella, and rickettsiae are also inhibited by relatively low concentrations. Corynebacterium diphtheriae, clostridia and listeria, and the treponema are highly susceptible. Though proteus, pseudomonas, Escherichia coli, aerobacter, and klebsiella species are relatively resistant to the drug in neutral to acid media, alkalinization markedly

Table 1. *In Vitro Spectrum of Erythromycin*

ORGANISM	MOST STRAINS
Streptococcus (pyogenic group)	0.04
Diplococcus pneumoniae	0.03
Staphylococcus aureus	0.4
Clostridium tetani	0.6
Corynebacterium diphtheriae	1.6
Neisseria gonorrhoeae	1.0
Neisseria meningitidis	3.12
Hemophilus influenzae	3.1
Hemophilus pertussis	0.2
Brucella	5.0
Escherichia coli	100.0
Aerobacter aerogenes	200.0
Klebsiella pneumoniae	> 200.0
Pseudomonas	> 200.0
Proteus	250.0
Salmonella	> 200.0
Shigella	100.0

increases its potency. Erythromycin has no effect on small viruses, most yeasts, or fungi.

Staphylococcal strains resistant to erythromycin may or may not show cross resistance with the other macrolides and lincomycin.[70] Actinomycetes, some species of mycoplasma, and trachoma viruses are susceptible to erythromycin. The antimicrobial activity of erythromycin is shown in Table 1.

MECHANISM OF ACTION. Erythromycin exerts its effect on bacteria by interfering at the ribosomal site where amino acids are transferred from amino-acyl soluble ribonucleic acid to protein.[77]

DEVELOPMENT OF RESISTANCE. Staphylococci have been shown to develop resistance to erythromycin. Five of eight staphylococci studied showed similar or slower rates of experimentally induced resistance than observed with penicillin.[82]

BACTERIOSTATIC AND BACTERICIDAL EFFECT. Erythromycin has a bactericidal activity against the highly susceptible pathogens: beta-hemolytic streptococci, pneumococci, and most strains of Staphylococcus aureus.[34, 37, 43] Its action is bacteriostatic against heavy inocula or less susceptible Staphylococcus aureus strains (Fig. 2).[31, 100]

ANTIBIOTIC COMBINATIONS

Herrell[49] observed that the combination of erythromycin and penicillin was markedly active against staphylococci resistant to each of the individual antibiotics. Waterworth,[106] Roberts,[86] and Oswald[78] confirmed Herrell's observations in vitro. Herrell[50] successfully treated penicillin-erythromycin-resistant staphylococcal infections using combinations of penicillin and erythromycin.
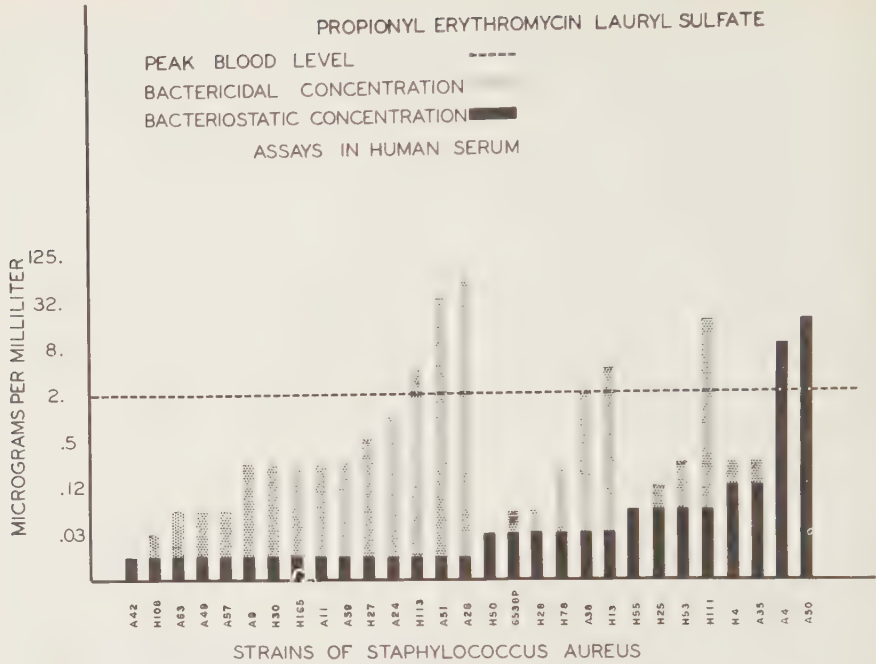
Figure 2.   Effect of erythromycin on Staphylococcus aureus strains.

ANIMAL PHARMACOLOGY

Lee[66] and Anderson[3] showed the difference in absorption and tissue distribution of erythromycin and erythromycin estolate after oral administration to rats (Table 2).

The antibacterial activity of the propionyl ester of erythromycin in vitro cannot be estimated accurately because of its rapid hydrolysis to erythromycin base in water solution. After it had been established that the ester/base ratio in mice was of the same order as in the human, Wick[107] compared the therapeutic effectiveness of each. The propionyl ester was shown to be more active in vivo and in certain experimental situations less active than the base (Table 3).

Table 2.   *Tissue Concentration of Erythromycin and Erythromycin Estolate, 2 Hours After Administration: Micrograms per Gm.*

	ERYTHROMYCIN	ERYTHROMYCIN ESTOLATE
Serum	2.6	0.7
Liver	33.0	4.4
Kidney	12.0	3.1
Lung	11.4	6.0
Heart	4.0	3.3
Brain	Trace	0.2

Table 3.   *Comparison of the Therapeutic Effectiveness of Propionyl Erythromycin and Erythromycin Base in Mice*

| INFECTION | ED$_{50}$ (mg. per kg.) | | | | TIME OF THERAPY |
| | SUBCUTANEOUS | | INTRAVENOUS | | |
	Propionyl	Base	Propionyl	Base	
Str. pyogenes	19	26	24	15	60 minutes postinfection
			29	40	120 minutes preinfection

Table 4.   *Acute Toxicity of Erythromycin in Mice*
[*Acute LD$_{50}$ (mg. per kg.)*]

INTRAVENOUS	SUBCUTANEOUS	ORAL
425	1849	2927

Erythromycin is poorly absorbed from the stomach in the rat but is readily absorbed from all parts of the small and large intestine.[66] The base is excreted in large amounts in the bile (approximately 15 per cent of the administered dose). In rats and dogs erythromycin is also converted to the des-N-methyl erythromycin which appears in the bile. This demethylation appears to take place at the microsomal level in the liver, yielding the des-N-methyl form.[67]

The toxicity of erythromycin for mice is shown in Table 4.[3] Tests in the rat, rabbit, and dog were in the low order of toxicity found in mice. Doses of approximately 40 mg. per kg. in the diet of rats and 220 mg. of erythromycin estolate per kg. given orally daily to dogs for 3 to 6 months did not alter their weight or cause alteration in blood counts or produce abnormalities in the liver or renal function.[5] Eighth nerve damage did not occur in cats given 50 mg. per kg. intramuscularly for as long as 2½ months.[3]

HUMAN PHARMACOLOGY

Erythromycin base and its salts are not consistently absorbed after oral administration, probably because of acid destruction in the stomach (since this effect is not seen in patients with pernicious anemia[36] or when unprotected base is administered with aluminum hydroxide[57]). This is in contrast with the reproducible and more persistent concentrations gained with erythromycin estolate. While food reduces absorption of erythromycin and its salts, it does not adversely affect (may even enhance) the absorption of the estolate form.[32, 53] Approximately 2 to 5 per cent of orally administered erythromycin preparations is excreted in the urine,[30] whereas 12 to 15 per cent is excreted by this route following intravenous erythromycin gluceptate.[28] Erythromycin does not diffuse readily across the normal meninges into the spinal fluid;[28] however, in patients with meningitis, assayable concentrations have been reported.[35]

Erythromycin traverses the placental barrier and produces assayable levels in the fetal circulation that are 6 to 20 per cent of the maternal value.[13, 60] Tissue levels have been largely related to serum levels. For instance, in ascitic fluid the concentration is 25 to 50 per cent of that found in the serum.[13] Adequate concentrations are also found in pleural fluid.[13] Erythromycin is concentrated in the liver, and in the bile the concentration is usually many times that of the serum. Hammond[41] reported less antibiotic activity in the bile following the administration of erythromycin estolate than when subjects were given erythromycin base. Erythromycin is consistently found in prostatic fluid and semen, and in these the level is approximately one third that of the blood level.[12, 112] Fecal excretion has been reported to be in the order of 320 to 640 micrograms per ml.[43]

Toxic amounts of erythromycin in man apparently have not been recorded. Doses of 7.0 and 8.0 gm. of erythromycin gluceptate have been given intravenously daily with no toxicity noted.[55] Johnson and Hurst[56] gave 2.75 gm. intravenously daily for 12 days to a 3 year old child with no signs of toxicity. Gastrointestinal disturbances in the form of epigastric pain, nausea, and mild diarrhea are the most common side effects with oral therapy. Diarrhea has been noted in ambulatory patients more frequently than in those confined to bed.[12] With very large doses, in the order of 8.2 to 12.6 gm. daily for 4 to 5 days, side effects occurred in 50 per cent of the patients and consisted of abdominal cramps, watery stools, decreased auditory acuity in one, and nausea and vomiting. Blood levels of 20 to 40 micrograms per ml. were obtained in 3 patients taking 8.0 gm. orally daily for 3 to 5 months with no evidence of toxicity. Depression of the bone marrow or alteration of liver or renal function was not found.[29] Supercolonization or superinfection with Monilia albicans is not commonly observed.

Braun[13] recently reviewed the infrequent reports of intrahepatic cholestatic jaundice in patients taking erythromycin estolate. Jaundice has not been reported with the base or its salts. Prodromal symptoms associated with the erythromycin estolate-induced jaundice are abdominal cramping with nausea or vomiting, or both. These symptoms are followed by jaundice, fever, leukocytosis, and eosinophilia. Unlike infectious hepatitis, the elevated bilirubin and transaminase values are usually associated with low or weakly positive tests of cephalin flocculation and thymol turbidity. Symptoms subside and the laboratory tests may return to normal within 3 to 5 days after stopping the antibiotic. A repeat course of therapy in patients manifesting these findings causes a return of the symptoms, fever, and laboratory findings, establishing this as a definite entity.

Kuder[65] reported an incidence of 2.5 per cent side effects, primarily gastrointestinal, with erythromycin estolate in a study including 10,377 children under the age of 16. Herrell[46] considered erythromycin the least toxic of the antibiotics generally prescribed.

Streptococcal Infections

The use of erythromycin in the treatment of streptococcal infections has established its effectiveness. Finland et al.[23] studied the susceptibil-

ity of beta-hemolytic streptococci to 11 antibiotics in vitro. Penicillin and erythromycin were the most active antibiotics against the 394 strains tested. Haight et al.[39] reported, in a clinical study of 114 patients with streptococcal respiratory infections, that 800 mg. of erythromycin daily for 7 days was more effective than only 3 to 5 days of therapy. In the 3 and 5 day treatment groups, the percentage of positive nose and throat cultures rose immediately after cessation of treatment and continued to rise to 45 per cent by the twenty-first day. The early elimination of streptococci suppresses the formation of anti-streptolysin O. The degree of inhibition of anti-streptolysin O is apparently related to the duration of antibiotic therapy.[39] It is for this reason that therapy must be continued for at least 10 days.

Haight[40] also found that erythromycin produced dramatic clinical improvement in scarlet fever. Two hundred and eight patients were divided into three groups. Seventy-eight patients were treated with erythromycin and received 1.2 gm. orally per day. Seventy-eight were treated with 300,000 units of procaine penicillin parenterally every 12 hours. The third group received placebo. There was no significant difference between the therapeutic efficacy of oral erythromycin and that of intramuscular procaine penicillin. Erythromycin was equally as effective as penicillin in preventing the suppurative complications that frequently follow this disease.

Other investigators have shown the effectiveness of erythromycin in the treatment of patients with acute pharyngitis and follicular tonsillitis due to Streptococcus pyogenes.[19, 48, 54, 72, 98]

The American Heart Association has recognized erythromycin as the alternate antibiotic for the treatment of streptococcal infections in patients with allergy to penicillin.[105] The American Dental Association also recommends erythromycin for prophylaxis when operative procedures are performed on penicillin-sensitive patients with a history of rheumatic cardiovascular disease.[2] The British Ministry of Health now recommends erythromycin instead of tetracycline as an alternate to penicillin in the treatment of streptococcal infections.[81]

Clinical evidence suggests that the presence of penicillinase-producing staphylococci in the nasopharynx may be responsible for decreasing the effectiveness of penicillin in acute streptococcal pharyngitis. Erythromycin administered along with penicillin in such cases has eradicated both staphylococci and hemolytic streptococci.[20, 99] Clinical studies of therapeutic response to different forms of erythromycin indicate that they are effective in streptococcal infections.[1, 9]

Pneumococcal Pneumonia

Most strains of Diplococcus pneumoniae are sensitive to the action of erythromycin preparations, and these medications have been used extensively in the treatment of pneumococcal pneumonia.[35, 38, 51, 104] Romansky[88] reported that 93 per cent of 213 pneumococcal pneumonia patients were effectively treated with erythromycin. Haviland[42] reported 60 cases of pneumonia treated with erythromycin. Both observed that results were similar to those obtained with penicillin. This same conclusion was reached by Austrian,[6] that erythromycin is generally con-

sidered to be as efficient as penicillin in the treatment of pneumococcal pneumonia. Pneumococcus strains resistant to penicillin or erythromycin are extremely rare in primary cultures.[64]

Mycoplasma Pneumonia

Mycoplasma pneumonia has been recently distinguished from a group of respiratory diseases known as primary atypical pneumonia, or viral pneumonia. Rasch and Mogabgab[53] treated 228 cases of Mycoplasma pneumoniae pneumonia. Their diagnosis was established by culture before treatment and by antibody response as indicated by complement fixation. An equal number of patients were treated with erythromycin and tetracycline. X-ray clearing was more rapid and the length of hospitalization was less than in the patients followed as controls. Mycoplasma pneumoniae have been shown to be much more sensitive to erythromycin in vitro than to tetracycline.[55]

Staphylococcus Infections

Erythromycin preparations have been used successfully in the treatment of a wide variety of staphylococcal infections, including pharyngitis, furunculosis, pyoderma, septicemia, urinary tract infections, postoperative empyema, wound infections, and ileocolitis.[17, 44, 79]

Finland et al.[24] compared the antistaphylococcal activity in erythromycin and other antibiotics. The incidence of antibiotic-resistant staphylococci is greater in hospitals than in outpatients. Hirsch[52] compared the antistaphylococcal activity of the sera of persons given 500 mg. single oral doses of erythromycin. He found the peak antibacterial activity was obtained 2 hours after ingesting the antibiotic, and the serum could be diluted on an average of as much as 32 times and still inhibit the staphylococcus. Antistaphylococcal activity was still present at the end of 24 hours.

Erythromycin used with other antibiotics has been shown to be effective in the treatment of staphylococcal bacteremia and endocarditis.[95]

Erythromycin, by virtue of its effectiveness, minimal side effects, and absence of disturbance of the bowel flora, is a useful drug in the treatment of staphylococcal infection so common in the newborn infant.[18] In staphylococcal empyema, erythromycin has been used intravenously and intrapleurally. It is claimed that when intrapleural injection (250 to 400 mg.) is combined with repeated needle aspiration, open drainage may be unnecessary.[68]

It is recommended that erythromycin be used with another antibiotic for staphylococcal infections that are slow to respond to therapy or where resistance may be encountered, such as endocarditis, osteomyelitis, meningitis and pyelonephritis. In addition, parenteral therapy may be indicated. Erythromycin can be administered parenterally in the form of erythromycin gluceptate or lactobionate, followed by oral therapy when this becomes feasible.[95, 96] Erythromycin has been shown by Herrell[17] to be highly effective in vitro and in staphylococcal infections when used with penicillin. Other in vitro studies have verified Herrell's observations.[82, 86, 106]

Hemophilus Infections

Strains of Hemophilus influenzae have been shown to be sensitive to erythromycin in concentrations of 0.5 to 3.0 micrograms per ml. and the activity of erythromycin in vitro against these bacteria is similar to that of the tetracyclines.[62, 69] Zinnemann[115] found H. influenzae strains highly sensitive, with few exceptions, to comparatively low concentrations of erythromycin. Pneumonia caused by this organism has responded rapidly to erythromycin therapy.[92] Nasou et al.[75] used erythromycin successfully in the treatment of a patient with H. influenzae pneumonia complicated by bacteremia. Romansky[88] reported that satisfactory responses were obtained in patients with H. influenzae meningitis and otitis media. Successful therapy of H. influenzae otitis media infections has also been reported.[93]

Pertussis

Though erythromycin has been shown to be more effective in vitro against Hemophilus pertussis than other antibiotics, including chloramphenicol, it has had limited clinical use.[15] Once the paroxysmal stage is reached, the clinical course is not noticeably changed by antibiotics other than in preventing or eliminating a bacterial superinfection.[76] Nelson[76] reported successful therapy of two patients with pertussis using erythromycin. Bass and his associates[3] showed that erythromycin therapy eliminated the pertussis organism. However, antibiotic therapy did not substantially modify the clinical course.

Diphtheria and Diphtheria Carriers

Diphtheria organisms are among the most sensitive to the action of erythromycin. Erythromycin has been used in the treatment of diphtheria without diphtheria antitoxin having been given at any time during therapy.[113] However, since antibiotics will not neutralize the previously elaborated toxin of the diphtheria organism, it is recommended that diphtheria antitoxin be combined with erythromycin therapy in the care of acutely ill patients. Beach and co-workers[5] used erythromycin in conjunction with diphtheria antitoxin in the treatment of 43 patients with diphtheria. In their study, erythromycin eradicated the Corynebacterium diphtheriae from the nose and throat of all patients in an average of 2 days. Blake[10] concluded that erythromycin is the most potent antibiotic for the treatment of diphtheria. Forbes[25] administered a 5 day course of erythromycin to 14 patients with diphtheritic infection. Although the bacteria had persisted through two courses of penicillin therapy, all patients responded to erythromycin. No virulent organisms were demonstrable 4 days after cessation of treatment. Haight and Finland[38] administered erythromycin to three carriers of virulent diphtheria bacilli who had consistently shown positive cultures during penicillin therapy. In each individual, at least three negative cultures were obtained at intervals of 1 to 3 days after the end of therapy. Blute[11] and Ricci[85] also used erythromycin successfully in the management of the diphtheria carrier state. Kempe[61] concluded that erythromycin "is the agent of choice in the treatment of patients with diphtheria or of diphtheria carriers."

Clostridium Infections

Bacilli have been eradicated from the wound site early in the course of tetanus, possibly because this organism has been shown to be more sensitive to erythromycin than to other antibiotics.[29, 58, 102] It is recommended that erythromycin be used in conjunction with antitoxin because the antibiotic has no effect on the tetanus toxin already circulating in the patient's tissues.

Additional Clinical Infections

Because the spectrum of erythromycin is wider than that of penicillin, it has been tried in clinical infections other than those listed above. Erythromycin has been shown to be effective in amebiasis.[4, 103] It can be used for the treatment of syphilis in those patients who cannot be given penicillin.[14, 73] Three patients with cervical fascial actinomycosis and one with actinomycotic perirectal abscess have been treated successfully.[15] Ninety-six per cent of the cases of gonorrheal urethritis responded to single doses of 2 gm. of erythromycin.[27]

Brucellosis has responded to erythromycin, especially the melitensis variety.[101] Chronic prostatitis infected with a variety of organisms showed improvement in 50 per cent of the cases following erythromycin therapy.[12] Winningham et al.[112] reported that erythromycin penetrates into prostatic secretions better than any of the other antibiotics studied.

Erythromycin has been used in conjunction with conventional therapy of pustular acne[87] and was shown to be effective in primary infections of the skin due to coagulase-positive staphylococci and beta-hemolytic streptococci.[17]

Erythrasma, a superficial infection of the skin that is often mistaken for dermatophytosis, associated with a gram-positive rod, Corynebacterium minutissimum, responds dramatically to erythromycin therapy,[63] as has nummular eczema. Because erythromycin is excreted in high concentration in the bile and its activity is enhanced against gram-negative bacilli in alkaline media, erythromycin base has been used successfully in the treatment of gallbladder and bile duct infections.[80]

Urinary Tract Infections

Zagar[111] showed that alkalinization of the urine enhanced the activity of erythromycin against bacterial gram-negative pathogens. Bucht[16] noted that E. coli and klebsiella infections responded to erythromycin, provided the urine was alkalinized. He reported that some urinary tract infections responded to erythromycin when they had been resistant to other antibiotics. Williamson and Zinnemann[111] found that of 347 strains of coliform bacilli studied, the majority were susceptible to concentrations that could be achieved in the urine. Recently Sabath et al.[90] and Zinner et al.[116] reported increased susceptibility of bacteria in alkaline media and the successful treatment of urinary tract infections in which other antibiotics could not be used. Guze[36] and Kalmanson[59] reported interesting observations in urinary tract infections in animals. Rats challenged with Streptococcus fecalis were treated with penicillin. Classical organisms were eliminated in the

urine but apparently protoplasts were found. When the animals were treated with erythromycin following penicillin, the protoplasts of Str. fecalis disappeared. Guze's work suggest that the administration of an antibiotic such as penicillin or cephalosporin, that produces defective bacterial cell walls, should be used in conjunction with erythromycin to eradicate the protoplast form and to achieve a higher per cent of "cure" with fewer relapses. The significance of Guze's findings needs further study. There are clinical reports that may be related to Guze's findings. Willcox[109, 110] found erythromycin effective in the treatment of nonspecific urethritis. Shepard[94] showed that a significant number of patients with nonspecific urethritis have a "T" strain of mycoplasma on culture of the purulent discharge.

DOSE AND DOSE FORMS

The dosage schedules recommended for the erythromycin preparations are shown in Table 5, and the preparations available for systemic therapy are listed in Table 6.

SUMMARY

Erythromycin has been shown to be effective in most of the commonly encountered bacterial infections of man. Its spectrum includes gram-positive cocci and bacilli, gram-negative cocci and, with alkalinization of the urine, gram-negative bacilli that are considered pathogens of the urinary tract. It is bactericidal, in concentrations achieved clinically, to the most susceptible organisms in its spectrum, with the bactericidal activity decreasing with less susceptible bacteria or in the presence of a heavy inoculum.

Erythromycin has a very low order of toxicity in animals whether administered orally or parenterally. In man gastrointestinal side effects, such as nausea, vomiting and diarrhea, may be a problem in 7 to 10 per cent, depending on the size of the oral dose. Reversible jaundice

Table 5. *Dosage Schedules of Erythromycin*

Children — Orally	
10–25 pounds	20 mg./lb./day*
25–50 pounds	125 mg. every 6 hours
Over 50 pounds	250 mg. every 6 hours
Adults — Orally	
Usual dose	250 mg. every 6 hours
Severe infection	500 mg. every 6 hours
Overwhelming infection	0.5–1.0 gm. every 6 hours, parenterally

*For more severe infections, 30 to 40 mg./lb./day in divided doses may be needed.
In overwhelming infections the dosage recommended for oral use can be given parenterally.
We usually administer antibiotics every 6 hours until the infection is controlled, and then shift to a more convenient "with meals and bedtime" (q.i.d.) schedule.

Table 6. *Preparations of Erythromycin for Systemic Use*

FORMS	CONCENTRATION OR SIZE	MANUFACTURER	TRADE NAME	COMMENTS
Oral				
Tablets	100 mg., 250 mg.	Abbott	Erythrocin	Film-coated stearate salt
Suspension	200 mg./5 cc.	Abbott	Erythrocin	Ethyl succinate, pediatric
Drops	100 mg./2.5 cc.	Abbott	Erythrocin	Ethyl succinate
Chewable tablets	200 mg.	Abbott	Erythrocin	Ethyl succinate, scored
Capsules	125 mg., 250 mg.	Lilly	Ilosone	Erythromycin estolate
Suspension	125 mg., 250 mg./5 cc.	Lilly	Ilosone	Erythromycin estolate
Drops	100 mg./cc.	Lilly	Ilosone	Erythromycin estolate
Chewable tablets	125 mg.	Lilly	Ilosone	Erythromycin estolate
Tablets	250 mg.	Lilly	Ilotycin	Acid-resistant coating erythromycin base
Tablets	100 mg., 250 mg.	Upjohn	E-mycin	Acid-resistant coating, erythromycin base
Parenteral				
Dry Powder	500 mg./20-cc. vial	Abbott	Erythrocin I.V.	Lactobionate salt
	1 gm. 30-cc. vial	Abbott	Erythrocin I.V.	Lactobionate salt
Solution	50 mg./cc. in 2-cc. and 10 cc. vials	Abbott	Erythrocin I.M.	Ethyl succinate, intramuscular
Dry Powder	250 mg./20-cc. vial	Lilly	Ilotycin I.V.	Gluceptate
	500 mg. 30 cc. vial	Lilly	Ilotycin I.V.	Gluceptate
	1 gm./50-cc. vial	Lilly	Ilotycin I.V.	Gluceptate

occurs infrequently in susceptible individuals taking the well-absorbed propionyl ester of erythromycin, but this has not been reported with other forms of erythromycin.

Because erythromycin does not require the renal route for excretion, it is probably one of the safest antibiotics for the treatment of systemic infections in patients with markedly reduced renal function.

Erythromycin is of value in the treatment of streptococcal and other infections in which the penicillins are contraindicated because of allergy. Staphylococcal infections usually seen in out-patient practice can be treated successfully with oral erythromycin. Severe staphylococcal infections requiring hospitalization should be treated with the parenteral form and used in conjunction with another antibiotic. Erythromycin has been shown to be particularly effective in vitro and clinically against staphylococcal infections when combined with the antistaphylococcal penicillins.

Erythromycin is of value in the eradication of the diphtheria and clostridia bacilli causing clinical infections.

Recent reports have shown, when the urine is maintained alkaline, that erythromycin is therapeutically effective in urinary tract infections even when due to gram-negative bacilli.

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Cephalosporins

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The cephalosporin antibiotics are semisynthetic antibacterial agents that are closely related, chemically, to the penicillins. The nucleus of 7-aminocephalosporanic acid is obtained from cephalosporin C which is elaborated by a fungus, Cephalosporium. At present there are two agents for parenteral administration currently in use. They are cephalothin sodium and cephaloridine, which are structurally similar, differing only in substitution of pyridine for an acetoxy group at position 3 (Fig. 1). Since both are poorly absorbed when administered orally, two other cephalosporin C derivatives, which are acid-stable, have been developed for oral administration. Cephaloglycin, a phenylglycine analogue of cephalothin sodium, is absorbed better after oral administration than cephalothin and cephaloridine, but not as well as a more recent desacetyl derivative of cephaloglycin, cephalexin (Fig. 1). Both of these agents have had extensive clinical trials but are not yet available for general use.

CEPHALOTHIN

Clinical Pharmacology

Intramuscular administration of cephalothin results in peak serum concentrations in 15 to 30 minutes.[62] In adults after 0.5 and 1.0 gm. doses, average peaks of 10 and 20 micrograms per ml., respectively, are observed.[5, 28, 63] Cephalothin concentrations plateau for the first hour, decline rapidly to about half the peak levels at 2 hours, and decline to low concentrations at 4 hours; after 6 hours there is little or no detectable activity.[62] A similar curve is seen in infants and children, except that in the first and second weeks of newborn and premature infants, respectively, detectable levels of antibiotic can be observed after 12 hours.[79]

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Intravenous administration of 1.0 gm. doses in adults results in concentrations varying from 2.5 to 40 micrograms per ml. at one hour, and 2.5 to 10 micrograms per ml. at 4 hours; 0.6 to 1.25 micrograms per ml. are still detectable at 6 hours.[91]

Cephalothin passes readily into pleural[45] and pericardial[30] fluids, with concentrations from one-half to twice that of serum, and into joint fluids with concentrations similar to serum levels.[30, 45] Intravenous administration of 1.0 gm. of cephalothin produces modest levels in ascitic fluid of 2 to 3 micrograms per ml. the first 3 hours, and 1 microgram per ml. through 6 hours.[90] High concentrations have been observed in skin, muscle, heart, stomach wall, liver, spleen, and kidney, with lesser concentrations in the brain.[63] In patients with inflamed meninges, spinal fluid has shown up to 50 to 75 per cent of concomitant serum levels.[28, 43, 49, 63, 68, 90]

Cephalothin is excreted predominantly through the kidneys by the renal tubules, and probenicid blocks tubular excretion. Excretion is rapid, and 60 to 90 per cent appears in the urine within 6 hours.[28, 45, 62] Peak concentrations after a single intramuscular 0.5 gm. dose average over 800 micrograms per ml. of urine, with correspondingly higher concentrations following larger doses.[45] About one-third of the drug appears in the urine as desacetylcephalothin,[45] following deacetylation in the liver. This metabolite has the same antibacterial spectrum of cephalothin but is one-half to one-sixteenth as potent.[94]

Preparations and Dosage

Cephalothin is packaged as a dry powder in 10 and 50 ml. ampules containing 1 and 4 gm., respectively. The powder contains 55 mg. of sodium per gram. For intramuscular injection, each gram should be diluted with at least 4 ml. of sterile water; lesser volumes will not allow proper solution. If not used relatively promptly, the solution
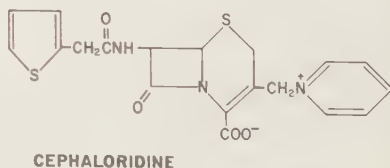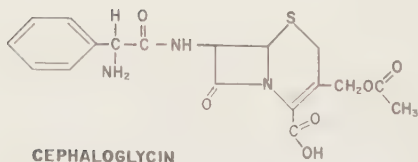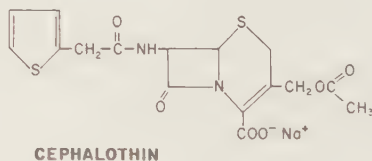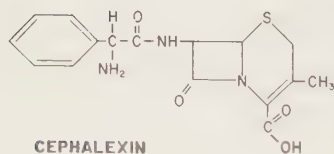
Figure 1.   Chemical structures of cephalothin sodium, cephaloridine, cephaloglycin, and cephalexin.

should be stored in the refrigerator but should not be used after 48 hours. For intermittent intravenous administration, 0.5 to 1.0 gm. in 10 ml. of normal saline may be injected slowly over a 3 to 5 minute period, or through the tubing when the patient is receiving parenteral fluids. For continuous intravenous administration the powder can be diluted in either 5 per cent dextrose or normal saline. In patients requiring high doses, the 4 gm. ampule is convenient for "piggyback" infusion by means of a Y-tube set. Frequent alteration of veins – that is, every 24 to 48 hours – and the use of scalp needles has been rewarded by a negligible incidence of thrombophlebitis in our experience.

The usual dose in adults is 0.5 to 1 gm. every 4 to 6 hours. In very severe infections 12 to 20 gm. a day have been employed.[13, 63] In children the usual dose is 40 to 80 mg. per kg. of body weight per day, while in premature and newborn infants 10 to 15 mg. per kg. per day is the recommended dose.

Adverse Effects

Pain after intramuscular injection is frequently noted by patients receiving doses of 1.0 gm. or more, particularly after repeated injections. Thrombophlebitis may occur after large daily intravenous doses, especially if veins are not alternated. Allergic reactions, including maculopapular rashes, urticaria, fever, serum sickness, and eosinophilia, are observed in about 3 to 5 per cent of patients.

Cross-allergy with non-penicillin antibiotics has not been conclusively demonstrated. It was hoped that cephalothin could serve as a substitute in penicillin-allergic individuals. A number of clinical investigations[28, 41, 43, 65, 68, 80, 92, 93] and our own studies[63] have rarely demonstrated untoward effects from cephalothin in penicillin-allergic patients. However, there have been reports of anaphylactoid reactions in four patients with backgrounds of penicillin hypersensitivity.[12, 37, 70, 76, 81] These reports, as well as certain observations in animals[3, 4] of cross reactions between penicillin and cephalosporin C derivatives conjugated to serum proteins, and demonstration of skin-sensitizing antibody to cephalosporins in a patient highly sensitive to penicillin,[27] suggest caution.[13] It has been suggested that the low incidence of severe reactions could be related to the observation that antibody in patients allergic to penicillin has less affinity for cephalothin than for penicillin.[76]

Direct Coombs' test reactivity has been observed in about 40 per cent of cephalothin-treated patients,[26, 57, 61] and in studies of normal monkeys.[61] However, to date there has been no clear-cut evidence of association of Coombs' reactivity after cephalosporin therapy with hemolytic anemia. Thus, at present, this observation relates more to the awareness that in cross-matching procedures, Coombs' tests may be affected by cephalothin therapy.

Clinical Indications

Cephalothin, like penicillin, is bactericidal and acts by interfering with cell wall synthesis. Since it must be given parenterally at least

4 to 6 times daily, it should be reserved for serious infections. This agent is unique in that it is effective against most gram-positive bacteria, and has potential usefulness in certain gram-negative infections.

GRAM-POSITIVE COCCAL INFECTIONS.   Since cephalothin is effective against both penicillin-sensitive and penicillin-resistant staphylococci, it is particularly valuable in patients with severe staphylococcal infections, including pneumonia, septicemia, endocarditis, meningitis, and osteomyelitis.[17, 28, 43, 51, 56, 63, 67, 92, 93]   Pneumococcal pneumonia[63, 87] and pneumococcal meningitis[63] are also amenable to therapy. Beta-hemolytic streptococcal infections, including septicemia and viridans streptococcic endocarditis,[63, 67, 87] have also been responsive to therapy, but enterococcic endocarditis has not been amenable to therapy.[67]

GRAM-NEGATIVE BACILLARY INFECTIONS.   There is wide variation in susceptibility of gram-negative organisms to cephalothin. Pseudomonas and indole-producing strains are highly resistant.

KLEBSIELLA-AEROBACTER INFECTIONS.   In many hospitals, no serious attempt is made to differentiate between Klebsiella and Aerobacter species. However, this differentiation is of importance since Klebsiella strains are usually susceptible to cephalothin, whereas Aerobacter species are frequently highly resistant.[50] Usually, if an organism described as "Klebsiella-Aerogenes" is nonmotile, it is sensitive to cephalothin, whereas motile strains are resistant. In our experience, pneumonias due to susceptible Klebsiella strains have responded.[63] High doses of at least 100 to 200 mg. per kg. per day are recommended for such infections.

ESCHERICHIA COLI AND PROTEUS MIRABILIS INFECTIONS.   Most of the clinical isolates of these microorganisms are susceptible to cephalothin. At times they may appear to be resistant by the disc method but susceptible by tube dilution tests. The high blood levels and particularly the high urinary excretion levels add to the effectiveness. This, plus the in vitro activity of cephalothin, has led to results equal to those observed with other agents commonly used in urinary tract infections due to E. coli or P. mirabilis.

CEPHALORIDINE

Cephaloridine differs from cephalothin in that it is an "internal salt," or betaine. As such it supplies its own cation in aqueous solution, and does not require either sodium or potassium in its formulation. Unlike cephalothin, cephaloridine is relatively painless upon intramuscular injection. It also differs from cephalothin, which is bound 55 to 60 per cent to serum proteins, by having little or no protein-binding capacity.

Clinical Pharmacology

Intramuscular administration of a single dose yields peak serum concentrations in 30 to 60 minutes. Intravenous administration yields peak concentrations in 15 minutes. Peak levels are almost double those observed with cephalothin, and decline of peak levels is much more

gradual, with significant concentrations still present 6 hours after a single dose (Fig. 2).[62] After continuous therapy or repeated doses, cephaloridine levels continue to rise, in contrast to the leveling off or relative equilibrium noted after cephalothin administration.[1, 86] In patients receiving 1 gm. every 6 hours, median serum levels of 50 and 15 micrograms per ml. are observed half an hour and 6 hours, respectively, after injection.[1] These differences are due to the greater stability of cephaloridine in the body and to differences in renal clearance; cephaloridine is cleared by the kidneys at about half the rate of cephalothin, and the serum half-life of cephaloridine is 1.5 hours as compared to 0.5 hours for cephalothin.[48, 11] Approximately 75 per cent of the administered dose is recovered in the urine, with very high concentrations evident during the first 8 hours;[12] median urinary concentrations of cephaloridine are approximately 50 per cent of the administered dose during the first 4 hours (Fig. 3).[62] There is evidence of some tubular excretion, since probenicid causes modest increases in peak serum levels and prolonged persistence of the drug.[39, 42]

As with cephalothin, cephaloridine diffuses into spinal,[1, 9, 24, 38] peritoneal,[24] and pleural[58] fluids.

Preparations and Dosage

Cephaloridine is packaged as a dry powder in 5 and 10 ml. ampules containing 500 mg. and 1 gm., respectively, and is readily dissolved in either saline or sterile water warmed to body temperature. The greater solubility of cephaloridine than that of cephalothin allows for smaller dilution volumes. Thus, for intramuscular injection, 2 and 2.5 ml. are usually employed for the 500 mg. and 1 gm. ampules,

Figure 2. Cephalothin and cephaloridine serum concentrations. Medians and ranges after 1 gram intramuscularly in a crossover study with 10 volunteers. (From Perkins, R. L., Saslaw, S., and Hackett, J. L.: Amer. J. Med. Sci., 253:293, 1967, reproduced with permission.)
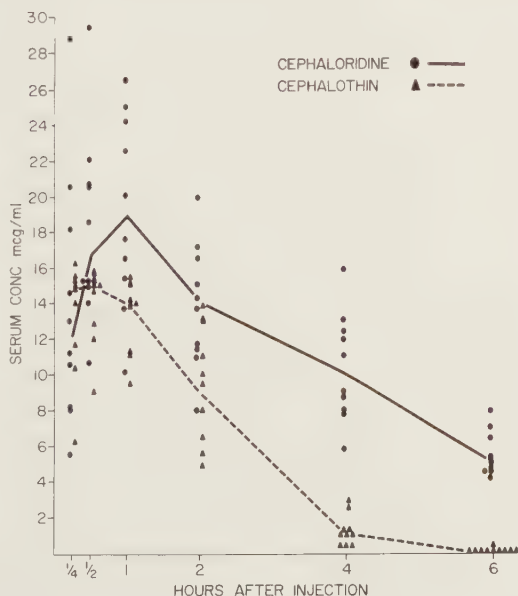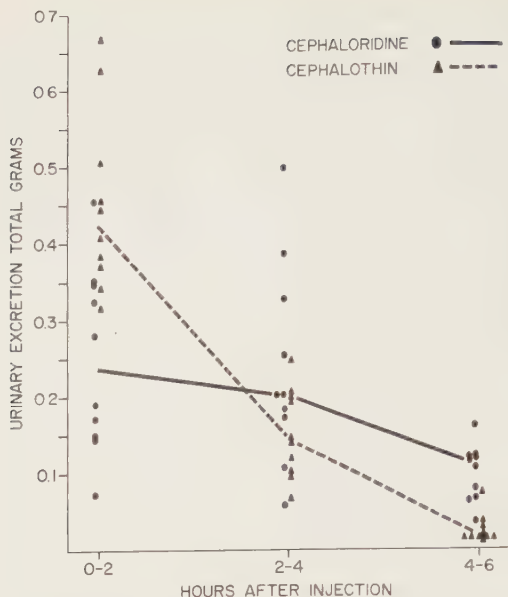
Figure 3. Cephalothin and cephaloridine urine concentrations. Medians and ranges after 1 gram intramuscularly in a crossover study with 10 volunteers. (From Perkins, R. L., Saslaw, S., and Hackett, J. L.: Amer. J. Med. Sci., 253:293, 1967, reproduced with permission.)

respectively. The usual dose in adults is 250 to 500 mg. 3 to 4 times a day. In severe infections, up to 1 gm. 4 times a day may be given, but potential nephrotoxicity suggests that doses not exceed 4 gm. a day. For intravenous use, 500 mg. or 1 gm. of drug can be dissolved in 5 or 10 ml. of diluent, respectively, for intermittent dosage, and given slowly over a 3 to 4 minute period through the tubing or directly into the vein. For continuous therapy the total daily dose may be dissolved in the fluid being administered; cephaloridine is compatible with normal saline or dextrose solutions. In children, 30 to 50 mg. per kg. per day for moderately severe infections, and up to 100 mg. per kg. per day for severe infections in 3 or 4 divided doses are employed.

Adverse Effects

The most significant difference between cephalothin and cephaloridine is the potential nephrotoxicity of cephaloridine. In our own experience[1] and that of others,[31, 39, 45, 81] acute renal failure occurred after administration of doses considerably higher than the present recommended maximum of 4 gm. a day. Acute renal failure has been reported, however, at this dosage in patients without known underlying renal impairment.[81] Studies in this laboratory[59] have shown that injections in rabbits and monkeys of 200 to 500 mg. per kg. per day resulted in marked alteration of renal function and necrosis of proximal tubules; 50 to 100 mg. per kg. per day did not cause renal injury. Elevations in blood urea nitrogen or creatinine have been observed in patients receiving recommended doses.[19, 31, 33, 39, 81, 85, 89] As in our studies with experimental infections in monkeys, this is usually reversible; an elevation of blood urea nitrogen seen early as a result of infection usually returned to normal during therapy as the infection subsided.[72, 73]

As with cephalothin, positive direct Coombs' reactions have been observed. In our experience 8 per cent of patients treated with cephaloridine exhibited positive reactions but no associated hemolytic anemia.[15] Whether the patient described as having a Coombs' positive hemolytic anemia, associated with acute renal failure after high doses of intravenous cephaloridine, represents a specific instance is not clear at this time.[39] Hemolytic anemia has been described in two patients with glucose-6-phosphate dehydrogenase deficiency in their erythrocytes.[85]

Allergic reactions are similar in nature and incidence to those observed with cephalothin, skin reactions and fever being the most common. Anaphylaxis has been described after intravenous cephaloridine therapy in a nurse who was able to tolerate penicillin.[10] The same question of cross-allergenicity with penicillin exists here as with cephalothin. Penicillin-allergic patients have received cephaloridine without untoward effects in some studies,[1, 9, 18, 20, 23, 36, 39, 47, 52, 71, 78, 81] while some allergic reactions have occurred in penicillin-sensitive patients.[18, 20, 25, 31, 34, 45, 58, 83]

Superinfections after cephaloridine as well as after cephalothin have been observed with particular reference to Pseudomonas, motile strains of Klebsiella-Aerobacter, E. coli, Proteus, Serratia, and Candida.[1, 33, 39, 81]

Patients receiving either cephalothin or cephaloridine may show false-positive reactions for glucose in the urine when tested with copper-reducing agents such as Benedict's solution, or Fehling's solution, or with Clintest tablets, but not with Tes-Tape.

Clinical Indications

Like cephalothin, cephaloridine is a broad spectrum antibiotic, and for practical purposes has a similar pattern of activity. Thus, it has been effective in staphylococcal,[1, 2, 5, 6, 8, 18, 21, 47, 54, 71] streptococcal,[1, 2, 9, 19, 34] pneumococcal,[1, 5, 8, 9, 18, 33, 83–85] H. influenzae,[1, 2, 8, 18, 19, 33, 34] gonococcal,[36, 52, 53, 55] E. coli,[5, 8, 10, 11, 18, 25, 47, 58, 88] indole-negative proteus,[8, 18, 22, 25, 78, 82] Klebsiella-Aerobacter,[5, 8, 18, 19, 34, 47, 78] and early syphilitic infections.[23, 77]

CEPHALOGLYCIN

Clinical Pharmacology

After oral administration, low but measurable concentrations in the blood, and high concentrations in the urine, are obtained. After 0.5 gm. doses, mean peak serum concentrations are 0.80 micrograms per ml. at 4 hours, and after 1.0 gm. doses they are 0.84 micrograms per ml. at 2 hours. Significant mean serum concentrations, ranging from 0.21 to 0.80 micrograms per ml., are still noted at 4 and 6 hours.[61] After 0.5 and 1.0 gm. doses, urinary concentrations during the 2 to 4 hour interval range from 60 to 282 micrograms per ml. and 58 to 1100 micrograms per ml., respectively. Mean urine concentrations of 35 and 83 micrograms per ml. are still observed over the 6 to 8 hour period after

0.5 and 1.0 gm. doses, respectively.[61] Cephaloglycin is excreted almost entirely as the active metabolite, desacetylcephaloglycin, and serum has no significant effect on the antibacterial activity of the antibiotic.[95] Cephaloglycin and its metabolite, desacetylcephaloglycin, has the similar antibacterial spectrum exhibited by the injectable cephalosporins.[95]

Preparations and Dosage

Cephaloglycin is supplied in 250 mg. capsules. It is also available for oral suspension in a 4 gm., dry, flavored mixture in 80 ml. packages which, when diluted, contain 250 mg. per 5 ml. For urinary tract infections in the adult, 250 to 500 mg. 4 times daily is the recommended dose. In children the usual daily dose is 25 to 50 mg. per kg. of body weight. Meals have little effect on absorption.[66]

Adverse Reactions

Diarrhea is the most common side effect, occurring in 3 to 15 per cent of patients. Allergic reactions in the form of rash or urticaria occurs in about 3 per cent of patients.[32, 35, 46, 69]

Clinical Indications

Cephaloglycin is indicated for the treatment of acute and chronic urinary tract infections caused by susceptible strains of E. coli, Klebsiella-Aerobacter, Proteus, staphylococcus, and enterococci.[7, 32, 35, 46, 61, 69]

CEPHALEXIN

The greater absorption of cephalexin as compared to cephaloglycin allows for a broader application of this agent in therapy. Our own experiences in clinical studies[16, 60] and in therapy of experimental streptococcal[73, 74] and staphylococcal[72, 75] sepsis in monkeys has demonstrated the potential efficacy of this agent. This preparation is discussed in detail by Griffith and Black in this issue.[29]

SUMMARY

The cephalosporins have become useful additions to the antibiotic armamentarium. Cephalothin and cephaloridine should be reserved for hospitalized patients with serious infections. Their application in gram-positive coccal infections and in selected gram-negative infections has been discussed. In addition, there are times when "blind therapy" must be started in acutely ill patients in whom sepsis is suspected. After obtaining suitable cultures, it has been our practice at times to use cephalothin in combination with kanamycin or gentamicin as initial therapy while awaiting outcome of culture results. This has been especially rewarding in patients with underlying disease or predisposing factors for sepsis.

Questions have been raised about the advisability of substituting cephalosporins for penicillin in the penicillin-allergic patient. In our experience, and that of many others described above, such patients have been treated without demonstrating any untoward reactions. However, the experience of others has emphasized caution. In any event, a patient with history of allergy to any antibiotic should not be treated with the cephalosporins for minor infections, and if they have serious infection and are treated with cephalosporins, the usual necessary precautions for handling severe reactions should be taken.

The potential nephrotoxicity of cephaloridine raises the point as to when it may or may not be used instead of cephalothin. In the following situations cephalothin would definitely be the agent of choice over cephaloridine:

1. Presence of azotemia, oliguria, or known pre-existing renal impairment.

2. Patients in whom depressed renal function may occur, as in shock, severe trauma, burns, hypovolemia, dehydration, and serious complicated surgical procedures.

3. Patients receiving other antibiotics with nephrotoxic potential.

4. Patients requiring high dosages or prolonged therapy, or both, such as in those with meningitis, endocarditis, or overwhelming infections.

5. Elderly patients who are more likely to develop renal function impairment.

6. Newborns, in whom the safety of cephaloridine has not yet been established.

In acute gonorrhea and early syphilis, the longer-acting cephaloridine is preferred. In all other situations the choice is based on the judgment of the physician in reference to each individual patient, with consideration given to pain, frequency of injection, and clinical status of the patient.

The role of the oral cephalosporins, as it appears to date, suggests that cephalexin may be employed in the future for mild to moderately severe infections as initial therapy or as a follow-up to previous initial parenteral therapy. The use of cephaloglycin will probably be confined predominantly to urinary tract infections.

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Cephalexin

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Cephalexin monohydrate, a new semisynthetic derivative of cephalosporin C, is a broad-spectrum bactericidal antibiotic which is well absorbed following oral administration. It is not significantly bound to serum protein and is excreted unaltered by the kidneys.

CHEMISTRY

Cephalexin, 7-(D-α-amino-α-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid, is compared, in Figure 1, with the structural formulas of the other cephalosporins which are either available commercially or under clinical investigation. Cephalexin contains the nucleus which is common to the other cephalosporins. It has a D-phenylclycyl group at the 7-amino position and is distinguished from all other cephalosporins by the simple methyl group at the 3-position.[7]

Two forms of cephalexin have been compared:

Form	Formula	Molecular Weight
Cephalexin (anhydrous)	$C_{16}H_{17}N_3O_4S$	347
Cephalexin monohydrate	$C_{16}H_{17}N_3O_4S \cdot H_2O$	365

The monohydrate produces higher blood levels and more immediate absorption after oral administration than the anhydrous form (Fig. 2).[10] For this reason, the monohydrate is incorporated in all cephalexin pharmaceutical forms.

Cephalexin is a zwitterion; i.e., the molecule contains both a basic group (the amino function on the acyl side chain) and an acidic group (the carboxyl at position 4 of the thiazine ring). Because of the presence of both, cephalexin exists essentially as an inner salt at physiological pH levels (pH 3–8). On either side of these values it begins to form a salt with external acids or bases.

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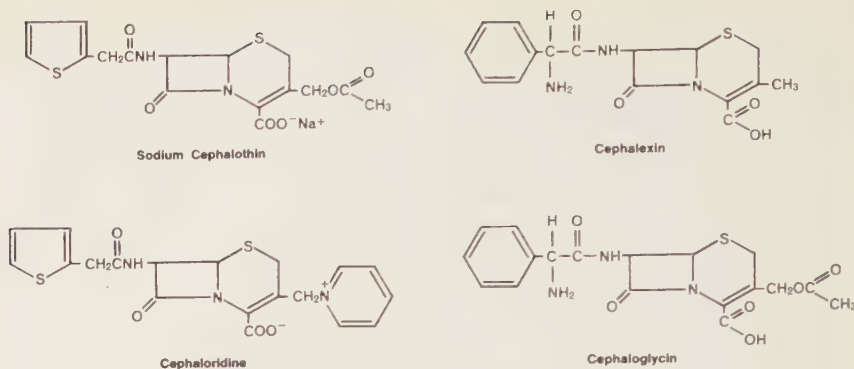
Figure 1.   Structural formulas.
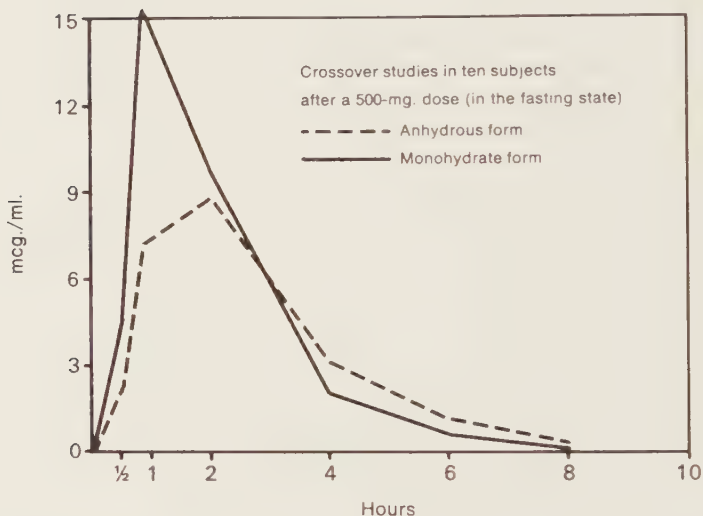
Figure 2.   Average serum concentrations with two forms of cephalexin.

Physical Characteristics

Cephalexin monohydrate is a white crystalline solid with bitter taste and faintly sulfurous odor. It has low solubility in water at room temperature; only 1 to 2 mg. may be dissolved easily in 1 ml. of water at 37° C. Solubility increases at either a low or a high pH (Fig. 3).[26]

Stability

DRY.   Cephalexin monohydrate is stable in the dry state as bulk powder, and pharmaceutical forms do not lose appreciable biological potency over a 2 to 3 year period at ambient (25° C.) or slightly elevated temperatures, e.g., 37° C.

IN SOLUTION.   Cephalexin stability in aqueous solution is a function of both pH and temperature. In general, the water solution of the drug
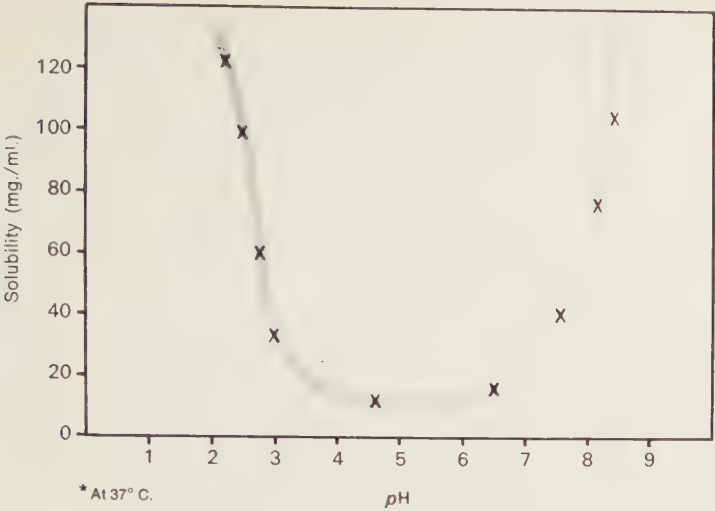
Figure 3.   Cephalexin monohydrate solubility vs. pH.

* At 37° C.
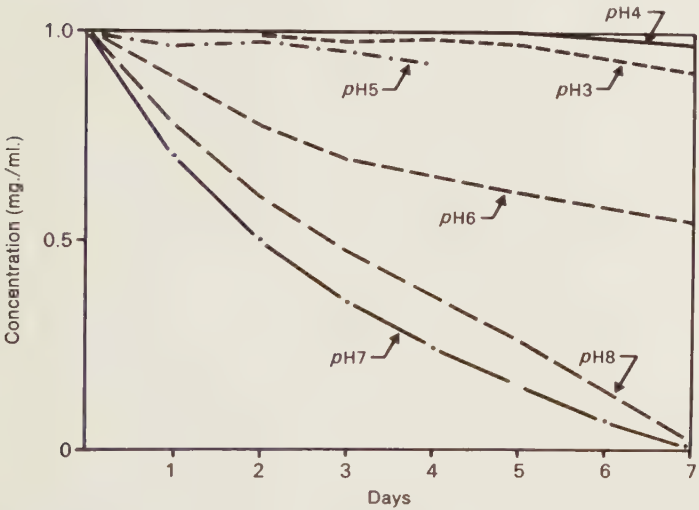
Figure 4.   Stability of cephalexin in buffered aqueous solution at room temperature (microbiologically assayed).

shows less deterioration at low pH or low temperature than at high pH or high temperature. In U.S.P. standard buffers at room temperature (25° C.), cephalexin is most stable at a pH of 4.5, its isoelectric point. Only slight degradation occurs after seven days. Figure 4 shows its deterioration rate at other pH values.[30]

Cephalexin is destroyed slowly in biological fluids, such as urine, serum, and spinal fluid. Table 1 shows that cephalexin is reasonably stable in biological solutions kept at refrigerator temperatures or in the frozen state.[19]

Table 1. *Stability of Cephalexin in Body Fluids*

Temperature (C.)	Half-Life in Serum (Days) Concentration		Half-Life in Urine (Days) Concentration		Half-Life in Spinal Fluid (Days) Concentration	
	(10 mcg./ml.)	(100 mcg./ml.)	(10 mcg./ml.)	(100 mcg./ml.)	(10 mcg./ml.)	(100 mcg./ml.)
37°	1.4	1.1	1.7	1.7	1.4	1.5
25°	2.9	2.5	6.3	4.4	2.4	2.7
5°	23	28.8	54	52	36	22.2
−20°	>90	>90	>90	>90	>90	>90

BACTERIOLOGY

A compilation of tube-dilution sensitivity data obtained by investigators is shown in Table 2.[5] Group A hemolytic streptococci, Streptococcus viridans, pneumococci, and Neisseria gonorrhoeae[29] and meningitidis are inhibited by concentrations that are achieved in the serum with 250 to 500 mg. doses orally. With light inocula, beta-lactamase-producing staphylococci are as sensitive to cephalexin as penicillin-sensitive staphylococci.[37] Methicillin-resistant strains are cross-resistant with cephalexin but not with cephalothin.[11] Of the gram-negative bacteria, most strains of E. coli, Proteus mirabilis, and Klebsiella are susceptible to the concentrations of cephalexin that can be obtained in the serum. There is a notable inoculum effect. Heavy inocula require more cephalexin for inhibition.[2] A few strains of Hemophilus influenzae are inhibited by

Table 2. *Number of Isolates Susceptible to Cephalexin — MIC (micrograms per ml.)*

Organism	Number of Isolates	<0.1	0.5	1	1.56	3.12	6.25	12.5	25	50	>50
Streptococcus (group A)	53	3	30	14	3	3					
Pneumococcus	18	3	4	7		4					
Streptococcus (viridans)	21		1	1	4	5	8	2			
Hemophilus influenzae	21					11	4	3		1	2
Staphylococcus (+) (−)	287		8	33	40	107	67	30	1		1
Salmonella	35			2	1	6	22	2			2
Shigella	40					6	17	10	3	4	
Proteus mirabilis	31					1	4	12	12	1	1
Proteus (indole-positive)	90					2	4	5	23	20	36
Escherichia coli	155					7	45	59	29	6	9
Klebsiella-Aerobacter	60					2	11	21	2	3	21
Klebsiella	68			1	2	11	14	19	10	4	7
Aerobacter	36						1	2	8	3	22
Enterococcus	78				2	2	3	3	1	7	60
Pseudomonas	85			1	1					1	82
Paracolon	8							1			7
Neisseria meningitidis	21			2	10	6	3				
Others	12					1	3	4	1		3
TOTALS	1,119	6	43	61	63	174	206	173	90	50	253

cephalexin. Many strains of enterococci, indole-positive Proteus, and Aerobacter bacilli are susceptible to the antiseptic concentrations that are found in the urine. Pseudomonas strains are universally resistant. It is possible to separate most Klebsiella from Aerobacter strains by the former's relatively high susceptibility to cephalexin.[41]

Bactericidal Activity

Wick[37] has also shown that cephalexin, in concentrations that can be achieved with the usual oral doses, is bactericidal against gram-positive and gram-negative bacteria in its spectrum (Table 3).

Protein Binding

The protein binding of cephalexin in human serum is 10 per cent in concentrations above 1 microgram per ml. Griffith and Black[10] have shown that cephalothin is approximately 25 per cent bound at this same concentration (Table 4). Other techniques have also shown binding of cephalexin to serum proteins.[13, 37]

Table 3. *Viable-Cell Counts from Tube-Dilution Sensitivity Tests with Cephalexin on Staphylococci and Gram-Negative Bacilli**

Bacteria	Strain	Tube MIC (mcg./ml.)					
		0	1.56	3.12	6.25	12.5	25
Staph. aureus	3055	10^9	10†	10	10	10	10
	3074‡	10^9	10^9†	10^4†	10	10	10
	3123	10^9	10†	10	10	10	10
	3125§	10^9	10^9	10^9	10^4†	10	10
	H43‡	10^9	10^9	560†	10	10	10
	H114‡	10^9	10^9	2,100†	10	10	10
	H232‡	10^9	10^9	10^4†	2,000	10	10
	S112‡	10^9	10^9	2,000†	10	10	10
Klebsiella-Aerobacter species	KA-14	10^9	10^9	10^9	10†	70	30
Esch. coli	EC-14	10^9	10^9	10^9	10†	10	10
Salmonella typhosa	SA-12	10^9	10^9	1,100†	10	10	10
Shigella flexneri 2b	SH-3	10^9	10^9	10^5†	10	10	10
Proteus species	PR-4	10^9	10^9	10^9	10	20†	130

*Inocula of 10^3 bacteria per ml. To eliminate inhibition by residual antibiotic, a 1:10 dilution was made prior to plating.
†Visual MIC.
‡Penicillin-resistant.
§Methicillin-resistant.

Table 4. *Per Cent of Protein Binding of Cephalosporins at Given Concentrations*

	Concentration (mcg./ml.)					
	0.2	0.4	0.8	1.6	3.2	6.4
Cephalothin		47%	41%	24%	18%	8%
Cephalexin	41%	20%	13%	9%	6%	

ANIMAL STUDIES

Table 5 summarizes the acute toxicity data for cephalexin.[36] There is a low order of toxicity in mice, rats, cats, dogs, and monkeys when the drug is given orally. Only after single oral doses of 2 to 4.5 gm. per kg. were employed in mice did lethargy and anorexia occur. Diuresis was also noted. A conservative estimate is that this amount of cephalexin given in a single dose is more than 30 times the therapeutic daily requirement for man.

Subacute and Chronic Toxicity

The long-term safety of cephalexin was demonstrated in 1 month studies in rats, dogs, and monkeys, and 1 year studies in rats and dogs.[36] The maximum daily doses of 1000 mg. per kg. for rats and 400 mg. per kg. for dogs and monkeys were well tolerated.

The only drug-related effects noted in rats were transitory growth suppression, slight diarrhea of short duration, and enlargement of the cecum and colon. The dogs developed transitory appetite suppression, salivation, emesis, and occasional diarrhea. There was no microscopic evidence of any adverse activity on the organ tissues, although blood concentrations were as high as 200 micrograms per ml. Salivation and moderate diarrhea were the only side effects observed in monkeys.

Intraperitoneal doses of 4 gm. per kg. in rabbits produced alteration of fecal flora as evidenced by diarrhea. Microscopic examination of renal tissue revealed slight vacuolar nephrosis in some animals.[36] (Cephaloridine produced a tubular necrosis in rabbits with doses of 200 mg. per kg.[35])

Intravenous doses of 15 to 60 mg. per kg. per day of cephalexin were well tolerated for 14 days by rats; dogs tolerated daily intravenous injections of 7.5 to 30 mg. per kg. No adverse effects were observed.

Studies in rats and mice following oral administration of cephalexin-^{14}C showed that the antibiotic is almost completely absorbed from the gastrointestinal tract and eliminated as unaltered cephalexin primarily in the urine. The serum half-life was estimated to be approximately 1.5 hours in rats and 45 minutes in mice after oral administration. Tissue concentrations in both species after orally administered cephalexin-^{14}C showed a wide distribution of cephalexin. Higher levels of the antibiotic were found in the kidney and liver than in the blood (Table 6).[32] Wells showed a half-life of approximately 25 minutes in these same animals.[5]

Table 5.   *Acute Toxicity of Cephalexin*

SPECIES	ORAL LD$_{50}$ (gm. per kg.)	INTRAPERITONEAL LD$_{50}$ (gm. per kg.)
Mouse	1.6–4.5	0.4–1.3
Rat	> 5.0	> 3.7
Weanling	> 4.0	
Newborn	> 3.0	
Rabbit		> 4.0
Cat	> 0.5	> 1.0
Dog	> 0.5	> 0.5 > 1.0
Monkey	> 1.0	

Table 6. *Cephalexin-¹⁴C Tissue Levels in Rats After a Single
Oral Dose of Cephalexin-¹⁴C (46 micromoles per kg.)*

TISSUE	1 HR.	4 HRS.
Blood	3.71	2.09
Liver	17.11	7.25
Spleen	2.21	1.45
Kidney	39.93	23.69
Lung	3.38	2.58
Heart	1.52	1.09
Fat	1.54	0.80
Muscle	1.16	0.76
Brain	0.53	0.24

Gager and his associates' reported penetration of cephalexin into the aqueous humor of the rabbit eye.

Physiological Effects

A large single intraperitoneal dose of cephalexin (500 mg. per kg.) had no significant cardiovascular effects in the cat.[36]

Oral administration in animals of 10 or 20 mg. of cephalexin per kg. produced slight increases in pyloric contraction for the first half hour after drug administration. Less effect was observed in the duodenal region. It was concluded that cephalexin had little effect on the musculature of the pylorus or duodenum and this could explain the low incidence of diarrhea reported.

Therapy of Experimental Infections in Animals

Wick[37] compared the minimal inhibitory concentration (MIC) of cephalexin in vitro to the in vivo curative dose (ED$_{50}$) (Table 7). Daily gastric administration of 100 mg. per kg. of cephalexin was compared to the same dose of cephaloridine given intramuscularly in the treatment of staphylococcal infections in monkeys; 3 of 8 receiving cephaloridine and 2 of 8 given cephalexin died, as compared to 7 deaths in the 8 untreated controls.[27] In similar studies, streptococcal infections that were sufficient to kill all the controls were cured with 12.5 mg. per kg. of cephaloridine parenterally. In the group of monkeys receiving 50 mg. per kg. of cephalexin per day, 2 of 8 died.[28] The staphylococci were

Table 7. *Activity of Cephalexin in the Test Tube and in
Experimental Bacterial Infections in Mice*

BACTERIA	STRAIN	MIC (micrograms per ml.)	ED$_{50}$ (mg. per ml.)
Staphylococcus aureus	3055	3.12	1.15
Staphylococcus aureus	3074	6.25	3.7
Streptococcus pyogenes	C203	0.5	1.8
Diplococcus pneumoniae	Type 1	3.12	58.2
Proteus sp.	PR-4	50	22.1
Klebsiella-Aerobacter spp.	KA-14	12.5	5.2
Shigella flexneri 2b	SH-3	6.25	<10
Salmonella typhosa	SA-12	12.5	15.6
Escherichia coli	EC-14	12.5	11.7

*Given in divided dose 1 hour and 5 hours post infection.

inhibited by 0.13 micrograms per ml. of cephaloridine and 3.9 micrograms per ml. of cephalexin. The group A hemolytic streptococci were more susceptible, requiring only 0.005 and 0.19 micrograms per ml., respectively, for inhibition.

CLINICAL PHARMACOLOGY

Cephalexin is not destroyed by gastric acids. It is completely absorbed in the upper portions of the gastrointestinal tract. After absorption, less than 10 to 15 per cent is reversibly bound to serum protein. Metabolic degradation is not extensive since virtually all of the antibiotic is recovered in the urine in the active form.

The average serum concentrations following single oral doses of cephalexin in fasting subjects are shown in Figure 5. Peak levels occur at 1 hour and persist for 4 to 6 hours.[11] These levels are comparable to those obtained with intramuscular injections of cephaloridine and cephalothin.[24] Braun et al.,[2] Thornhill et al.,[33] Muggleton et al.,[22] and Kunin and Finkelberg[15] found blood levels that were slightly lower than those reported by others.[3, 9, 11, 13, 21, 25] Lower peak values may be related to the time food is ingested and to the dose of the antibiotic (Fig. 6). When cephalexin is administered with food, there is a delay in onset of absorption, a lower peak and a prolongation of the blood levels.[11]

The average urine excretion, determined in fasting subjects, ranged from 75 to 100 per cent of the administered dose (Fig. 7).[2, 3, 9, 11, 13, 21, 24] The total amount of cephalexin excreted in the urine over an 8 hour collection period was 50 to 100 per cent when ingested with meals (Fig. 8).[2, 11, 21, 22]
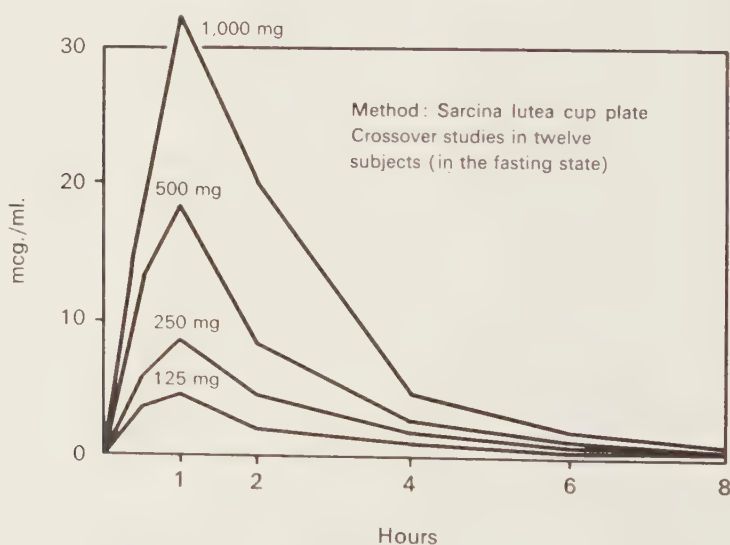
Figure 5.   Cephalexin blood levels with increasing dosage.
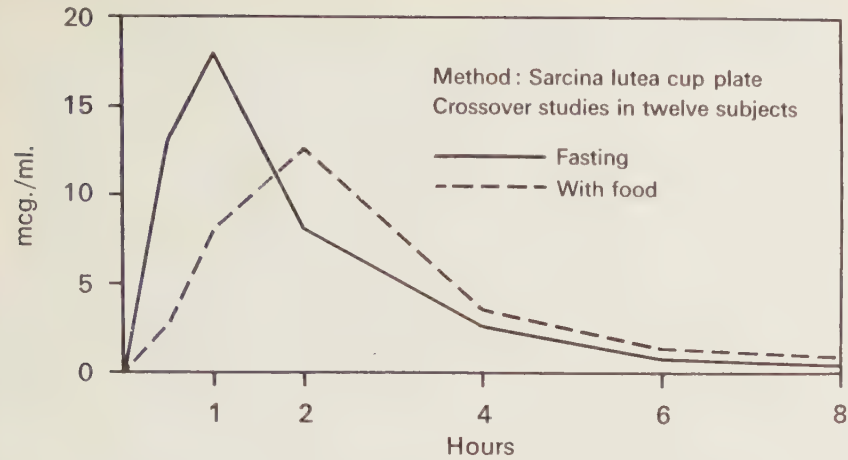
Figure 6.   Effect of food on cephalexin blood levels (500 mg. dose).
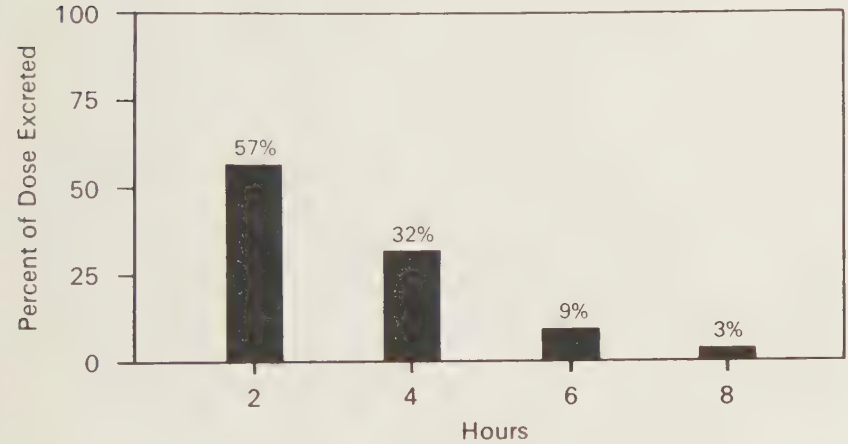
Figure 7.   Cephalexin urinary excretion.
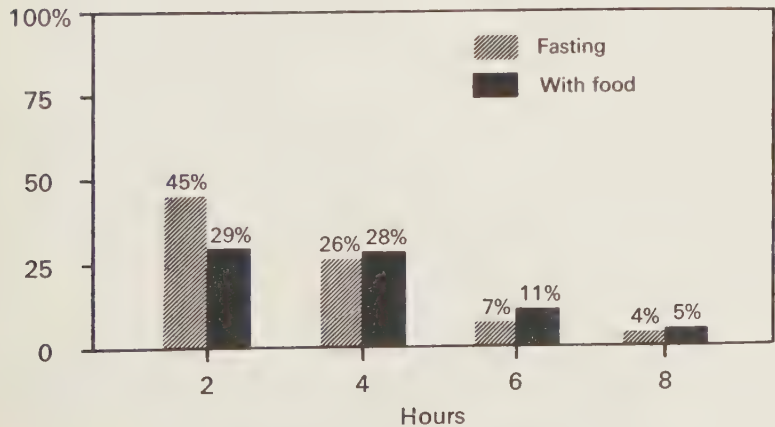
Figure 8.   Per cent of dose excreted (500 mg. dose).

Apparently cephalexin is excreted both by the glomeruli and tubules of the kidney. Administration of probenecid to block tubular excretion produces higher and more prolonged blood levels, and the rate of clearance by the kidneys is slowed, suggesting conversion from both glomerular and tubular excretion to primarily glomerular clearance.[2, 9, 11]

The clearance of cephalexin from the serum of patients with reduced renal function may be prolonged.[10] Kunin and Finkelberg[15] administered cephalexin to patients with reduced renal function. "Uremic" patients had serum concentrations two to three times those in normal subjects with only modest accumulation over the treatment period (Table 8).[15] In anuric patients requiring maintenance hemodialysis, a single 250 mg. dose of cephalexin produced sustained levels of 20 to 24 micrograms per ml. for 24 hours. Dialysis for 20 to 60 minutes dropped the serum levels 50 per cent, approaching the extraction rate of creatinine.[12]

Other Pharmacologic Studies

The effect of large doses and prolonged therapy has been studied. Griffith and Black[10] gave 4 gm. of cephalexin daily for 1 month to 12 volunteers, and Maibach[18] conducted a similar study in 40 subjects. Before, during, and after medication, data were obtained from a battery of laboratory tests. Ampicillin in equal dosage was used as a control. The findings remained essentially normal although some fluctuation of values was observed. There was no significant difference in hematologic, hepatic, or urinary status when the cephalexin data were compared to the results obtained in subjects receiving ampicillin.

Eleven normal subjects were given 8 gm. of cephalexin daily for 2 weeks. Laboratory tests showed no significant change in blood, renal or hepatic function. Blood concentration and urine excretion studies showed no evidence of accumulation in these subjects (Fig. 9).[10]

Gager et al.[8] and Boyle et al.[1] showed adequate therapeutic concentrations in the aqueous humor following single oral doses of 1 to 2 gm. of cephalexin.

Table 8.   *Comparison of the "Peak" and "Valley" Levels (micrograms per ml.) at the Beginning and End of Therapy with 500 mg. of Cephalexin Every 8 Hours in "Uremic" Patients*

PATIENT	CREATININE CLEARANCE (ml. per minute)	PEAK		VALLEY	
		1st day	8th day	1st day	8th day
1	4	15		15	
2	9.2	19	50	17	8
3	12.3	19	30	15	25
4	13.5	7	32	3	15
5	15.2	16		12	
6	32.1	4	12	2	7
7	33.8	12	12	4	4
Average		13	27	8	12
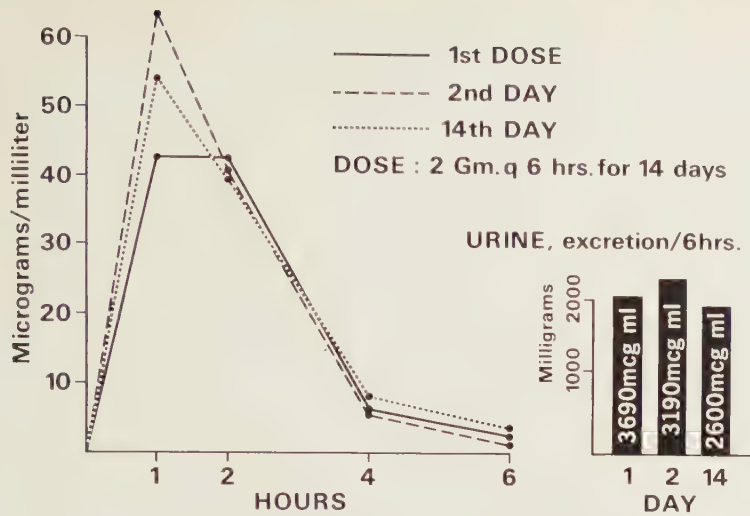
Figure 9.   Comparison of cephalexin blood levels.

CLINICAL THERAPY

The in vitro susceptibility of the commonly encountered bacteria (see Table 2) and the high bactericidal serum and urine concentrations obtained after oral administration of cephalexin (Fig. 5) indicated that clinical trials should be conducted in the treatment of infections due to these pathogens. The published clinical results of therapy in 444 patients available at this writing are shown in Table 9.

Table 9.   *Clinical Results of Therapy with Cephalexin*

INFECTION	REFERENCE	NO. OF PATIENTS	DAILY DOSE	SUCCESS RATE (per cent)
Streptococcal pharyngitis	31	39	0.5 gm.	90
	16	94	20–25 mg/kg	94
	6	6	1–3 gm.	83
Lobar pneumonia	29	25	2–4 gm.	92
	6	12	3–6 gm.	83
Soft tissue (staphylococcal)	23	25	2 gm.	96
	6	29	2–4 gm.	86
Urinary tract infection	34	78	1.0 gm.	83
	17*	23	2.0 gm.	43
	13*	5	3–6 gm.	40
	6*	8	2–4 gm.	25
	4	100	1–6 gm.	85

*Majority of patients (chronic, complicated, prior antibiotic failures) clinically improved but had bacteriology relapse or "super-colonization" related to cessation of therapy.

Table 10. *Respiratory and Soft Tissue Infections*

DIAGNOSIS	NO. OF PATIENTS	SATISFACTORY*	CLINICAL SUCCESS RATE
Respiratory			
Beta strep pharyngitis			
and tonsillitis (children)	202	196	97%
Otitis media†	14	13	95%
Acute bronchitis	62	38	61%
Chronic bronchitis	9	4	44%
Pn. pneumonia†	98	80	81%
Soft Tissue			
Cellulitis	41	40	98%
Pyoderma	26	25	96%

*Successful results both clinically and bacteriologically.
†Cultures not obtained in some (children).

In a comparative study using oral penicillin and cephalexin in equivalent doses, cephalexin was equal or superior to penicillin V or ampicillin in eradicating group A hemolytic streptococci.[31] It is apparent that acute infections of the urinary tract[4, 34] respond to therapy better than do chronic infections.[6, 13, 17] Of the 25 cases with lobar pneumonia reported by Seftel et al.,[29] six had more than one lobe of the lung involved. Typically, many of the patients were malnourished alcoholics. One of the two failures had three lobes of the lung involved. This same investigator successfully treated a 35 year old man with tonsillar diphtheria using 3 gm. of cephalexin the first day and 1.5 gm. for 4 days.[29] Single cases of staphylococcal septicemia[13] and endocarditis[15] have responded to oral cephalexin.

The case reports submitted by the investigators participating in the clinical trial of cephalexin have been computer-tabulated.[5] Because of its almost complete oral absorption, cephalexin has been used primarily to treat the types of infections encountered in typically outpatient practice where the other orally administered broad-spectrum antimicrobials (ampicillin, tetracycline, chloramphenicol, and sulfonamides) have been found useful. Patients who received more than 4 gm. per day or those treated with concomitant antibiotics were not included in Tables 10 and 11. The causative organism was isolated at the start of cephalexin therapy from all cases included in these tables; susceptibility to cephalexin was established (the antibiotic is not recommended for the treatment of cephalexin-resistant organisms); and follow-up cultures were obtained when possible (healed pyodermas and cellulitis follow-up cultures were considered meaningless). Acute infections due to gram-positive bacteria responded well to cephalexin therapy but chronic infections, i.e., bronchitis and pyelonephritis, did not. These results are similar to those obtained with other antibacterial agents.[13]

SIDE EFFECTS

All patients treated with cephalexin, regardless of diagnosis, duration of therapy, or concomitant treatment with other antibiotics or agents, were included in the tabulation of side effects (Table 12).[5]

Table 11. *Urinary Tract Infections*

DIAGNOSIS	NO. OF PATIENTS	SATISFACTORY*	SUCCESS RATE
Acute			
Cystitis	108	101	94%
Pyelonephritis	55	50	90%
U.T.I.	57	48	84%
Total	220	199	90%
Chronic			
Cystitis	52	45	86%
Pyelonephritis	58	43	74%
U.T.I.	71	53	75%
Total	181	141	78%
Prostatitis			
Acute	35	34	97%
Chronic	10	8	80%
Total	45	42	89%

*Successful results both clinically and bacteriologically.
†Meaningful culture not obtained in some patients.

Table 12. *"Major" Side Effects in 1671 Patients*

	TOTAL	PER CENT OF TOTAL	DRUG RELATED	THERAPY STOPPED	PER CENT OF TOTAL
Diarrhea	41	2.5	21	10	0.6
Nausea c/s vomiting	23	1.4	9	11	0.66
Rash	13	0.8	6	5	0.3
Vomiting	9	0.5	3	4	0.24
Possible allergic reaction	1		?	1	
Pruritus	3		1	0	
Urticaria	2		1	2	
Angioedema	1		1	1	
Dermatitis	1		0	1	
Diplopia	1		?	1	
	95	6.0	44	36	2.0

Diarrhea was the most commonly encountered side effect. However, in the total of 1671 patients, diarrhea was severe enough in only 10 to warrant stopping therapy. Approximately an equal number had nausea, four with vomiting. Findings suggestive of allergy, rash, urticaria and dermatitis, were of enough concern to terminate therapy in four patients. One child had angioneurotic edema of the lips. A total of 0.6 per cent allergy was considered a relatively low incidence even for an oral antibiotic.

A patient who gave a history of allergy to penicillin and knew she was receiving a new test antibiotic had palpitation and light-headedness. The medication was stopped. Cross-allergy to penicillin, though suggested, could not explain her similar reactivity to sulfa.

Table 13. *"Minor" Side Effects in 1671 Patients*

	TOTAL	DRUG RELATED	THERAPY STOPPED
Possible monilia			
Pruritus ani	3	2	0
Pruritus, genitalia	4	4	0
Monilia, genitalia	5	4	2
Monilia, gastrointestinal	1	1	0
Vaginitis	3	3	2
Vulva discharge	3	1	1
Intertrigo	2	2	0
Gastrointestinal			
Pancreatitis	1	0	1
Anorexia	2	0	0
Dyspepsia	5	4	1
Flatulence	1	0	0
Eructation	1	0	0
Abdominal pain	5	1	1
Central Nervous System			
Dizziness	4	1	1
Fatigue	2	1	0
Headache	4	1	2
Pressure in ears	1	0	0
Other			
Fever	1	0	1
Alopaecia	1	0	1
Aggravated varicose vein	1	1	0
	50	26	13

Mild untoward reactions were noted in 50 patients (Table 13). Therapy was discontinued in only 13 of these. Pruritis of the perineal area possibly was associated with monilia, though the organism was not cultured. In only five patients did pruritis cause cessation of therapy.

The remainder of mild reactions were of less significance except for single reports of pancreatitis and fever. The pancreatitis was an acute exacerbation that occurred in a patient with known chronic pancreatitis. Falling hair (alopecia) noted after a few days of therapy in one patient could not have been related to cephalexin. The fever reported was believed to be drug fever since it recurred on challenge.

Thirty-one of the 1671 patients died while receiving cephalexin therapy or shortly thereafter. None of the investigators believed cephalexin was related to their demise. For example, a patient reported to have thrombocytopenic purpura while on cephalexin had this condition prior to cephalexin therapy; he developed empyema of the gallbladder and peritonitis, and ultimately died.

SUMMARY

Cephalexin is a new semisynthetic cephalosporin antibiotic. It has a broad bacterial spectrum, including group A hemolytic streptococci, pneumococci, penicillin-susceptible and penicillin-resistant staphylo-

cocci, gonococci, most strains of E. coli, Klebsiella, and indole-negative Proteus. Cephalexin is bactericidal against the gram-positive and gram-negative bacteria in its spectrum. Serum inactivation or protein binding of cephalexin is low—less than 10 to 15 per cent.

After oral administration cephalexin is completely absorbed, and virtually all of the dose is excreted in the urine. Clearance by the kidneys apparently includes both glomerular filtration and tubular excretion since it has been shown that tubular excretion can be blocked by probenecid. If cephalexin is given along with meals, there is some delay in onset of absorption, and peak levels are lower but more prolonged. Similar quantities of cephalexin are excreted in the urine but over a longer period of time when the cephalexin is administered with food rather than when fasting.

In daily doses of 1 to 4 gm. in adults and 25 to 50 mg. per kg. in children, cephalexin has been used successfully to treat streptococcal pharyngitis, pneumococcal pneumonia, staphylococcal soft tissue infections, and acute urinary tract infections. Chronic urinary tract infections have a lower incidence of bacteriological cure and a higher incidence of relapse than acute infections. The results in chronic urinary tract infection are characteristic of those obtained following the use of other antibiotics and chemotherapeutic agents.

The incidence of side effects has been notably infrequent, including those referable to the gastrointestinal tract, even though the antibiotic is administered orally. The incidence of 0.6 per cent allergy, manifested primarily as rash or urticaria, was considered low even for an oral antibiotic.

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Kanamycin

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Kanamycin has been available for clinical use since 1958. It proved to be, and still is, an exceedingly powerful antimicrobial agent, often the first choice drug for therapy of life-threatening infectious diseases. Its main use is for the drug management of common, severe gram-negative bacterial diseases, including sepsis. Its prescription must be made with discrimination, for inherent in its administration is the danger of a unique damaging effect upon the cochlear branch of the eighth cranial nerve, leading to irreversible deafness. In the 12 years of its clinical use, extensive knowledge about its properties has become available;[11, 21] this report attempts to review its efficacy and its limitations and proffers suggestions about its safe administration to humans. Four years ago, this author described the following as being appropriate for the drug:[3]

> Does it ever strike you
> That the more we see of you
> The more we like you
> H. BELLOC: "On No Man the Guest," 1920

Considering its usefulness versus its capacity to produce unfortunate side effects, the same opinion can be reaffirmed, remembering that even "friends" can be harmful and provoking.

In general terms kanamycin has two amino sugars glycosidically linked to deoxystreptamine and is commercially available as the sulfate.[14] It is chemically quite closely related to neomycin, streptomycin, paromomycin, and gentamicin. It has a broad spectrum of antimicrobial activity, including major inhibiting effects upon tubercule bacilli, staphylococci, Neisseria, and some other gram-positive cocci, as well as most of the gram negative bacilli.[6, 9, 15, 20] Neither primary nor acquired resistance has been a major deterrent to its continued clinical use.[1, 6, 7] It is a true poison to many bacteria, but unfortunately to some important human cells as well. Consequently, in almost all instances it is a therapy to be administered only in the hospital.

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ROUTE OF ADMINISTRATION

Kanamycin should be used parenterally only. Its administration by the oral route has been studied carefully, and there is virtually no advantage to its prescription by this route even in the therapy of intestinal diseases caused by susceptible bacteria.[1, 10] Absorption from the gastrointestinal tract is minimal and although the basic chemical has been modified by a number of additives, such as 3-phenyl salicylate, these have not improved absorption significantly. Therefore, for the management of both local and systemic infectious diseases, this route of administration is more or less worthless. As a preoperative preparation given orally or in the management of liver failure through its deleterious effect upon growth of urea-producing bacteria in the bowel, it is far less efficacious than its relative neomycin.[10]

Accordingly, kanamycin is a drug to be used almost exclusively parenterally, generally by the intermittent, intramuscular route. Intravenous use is feasible, but is uncommonly needed. The preparation has harsh effects upon veins, its use in intravenous fluids is frequently incompatible with other needed agents, and the need for intramuscular doses more often than three times daily is rare. It must be emphasized that the drug does not mix well with other chemicals and, therefore, should be administered intramuscularly or intravenously alone; it should be given in isotonic saline.[2] If used intravenously, a solution of 2.5 mg. per ml. of diluent is recommended – or 0.5 gm. in 200 ml.

PHARMACOLOGY AND TOXICITY

Following a single intramuscular dose, detectable levels in blood are observed after 15–30 minutes and peak concentrations occur within 2 hours.[18, 21] A single intramuscular dose of 1 gm. of kanamycin is followed by peak levels above 30 micrograms per ml. With a 0.5 gm. dose, highest concentration in serum is about 20 micrograms per ml., and after 0.25 gm., the peak is 12 micrograms per ml. Thereafter, there is a rapid fall of levels for 4 to 6 hours, albeit low levels (1 to 4 micrograms per ml.) are still present at 12 hours (Table 1). Half-life in serum thus is 4 to 6 hours, and no cumulative effect is observed in individuals

Table 1. *Serum and Spinal Fluid Levels of Kanamycin After a Single Dose of 7.0 mg. per kg.* *

	HOURS AFTER DOSE						
	1	2	3	4	5	6	12
Blood levels (micrograms per ml.)	18	15	12	6	4	3	1
Spinal fluid levels (micrograms per ml.) – Normal	1	1	2	4	3	2	1
Spinal fluid levels (micrograms per ml.) – Meningitis	2	5	8	9	8	7	4

* After Eichenwald.[8]

with essentially normal kidney function who receive sensible doses every 6 to 12 hours. In children over the age of 3 months, levels in blood are similar to those in the adult depending upon the dose given, i.e., from 100 to 250 mg.[8, 11, 13, 26, 29] Peak levels (± 15 micrograms per ml.) in children are achieved with doses of 5 to 10 mg. per kg. daily, which are from three to five times the amounts generally needed for maximal antibacterial effects, as measured by *in vitro* sensitivity testing.

Distribution of the drug into various body tissues follows a pattern not unlike that of penicillin. Concentrations of kanamycin in kidney and liver are similar to those in blood. Lower levels are attained in bone, skin, and heart muscle.[18] Concentrations in spinal fluid are low, but do reach peaks after 3 to 5 hours (as the blood levels fall) in the uninflamed meninges.[18] With meningitis, more crosses the blood-brain barrier (Table 1). Low concentrations are measurable in stool and bile, so that enterohepatic recirculation is minimal. Kanamycin penetrates, after a standard parenteral dose, into all body fluids – synovial, bile, pleural and peritoneal – but, as with the central nervous system, it does not cross well the blood-amnion barriers.[2]

Kanamycin is excreted in the urine as the active drug and from 50 to 75 per cent of a single dose can be recovered in the first 24 hours.[18, 24] Thus, concentrations in urine with any therapeutic regimen are high. Levels above 100 micrograms per ml. in urine are observed for 12 hours after a 0.25 gm. dose; with a 0.5 gm. dose, more than 300 micrograms per milliliter. It is excreted by glomerular filtration with a mean clearance rate of more than 75 ml. per minute. Nothing is known about the fate of that fraction of kanamycin that cannot be recovered from the urine in its free form.

Untoward reactions to kanamycin occur. They include ototoxic effects, first recognized by tinnitus and then by loss of high-frequency hearing. This will be discussed later in more detail. Nephrotoxicity is, in the early phases, characterized by the appearance in the urine of casts, albumen, and a few red and white cells. As a general rule the renal lesions produced by the drug are irritative only and become totally reversible upon its cessation. If the indications are appropriate, the drug can be continued in the face of these urine changes, for permanent damage to kidneys is not anticipated. This is a secure statement, for duration of therapy with kanamycin is restricted because of its other toxicities. Nephrotoxicity, thus, is of minor clinical importance.

Allergies are quite uncommon, but when they do occur, they are like those observed after the administration of very many other chemotherapeutic agents. Eosinophilia is usually associated. As is true with other aminoglyosides, the incidence of hypersensitivity reactions is well below 5 per cent. When they appear they deserve symptomatic treatment only – rarely has anaphylaxis been observed.

A unique and again very rare characteristic of the aminoglycoside family is the development of neuromuscular paralysis, with respiratory depression. This occurs generally only after intraperitoneal administration.[2] Mostly it happens while the patient is still under anesthesia and particularly so if other muscle-relaxing drugs have been given. It

is recommended that intraperitoneal kanamycin be used only at a time when the patient is out from under the effects of anesthesia. In fact, its intraperitoneal administration is rarely indicated.

As is true with any potent bacteriocidal agent, superinfections do occur after the use of kanamycin.[3, 6, 23] Such can be expected in the situation where the primary offending pathogens have been killed prior to the resolution of the underlying inflammatory disease. Another kind of microbe settles into the damaged tissue before the host can control it and, predictably, the new invading organism is resistant to kanamycin. This, when it happens, generally occurs after 4 to 7 days of therapy with kanamycin and often requires a shift in the antimicrobial regimen.

Sensible dosage scheduling of kanamycin depends mainly upon the status of the patient's kidney function, and unless the regimen is carefully designed, ototoxicity is far more likely to occur than is warranted. Kanamycin is retained in the serum of patients with renal disease. In the normal patient, the half-life of the drug is 4 to 6 hours.[18, 19, 21, 22] In the uremic patient, it is as long as 72 hours. Thus, to achieve as safe and comparable levels in the patient with kidney damage as in normal subjects, the following recommendations should be followed: oliguric patients should receive a loading dose of 1 gm. of kanamycin by the intramuscular route followed by injections of 0.5 gm. at intervals of 2 to 4 days. Patients recovering from the oliguric phase of acute tubular necrosis or uremic patients whose glomerular filtration rate is estimated at greater than 10 ml. per minute, should receive the same loading dose and repeat doses of 0.5 gm. at intervals of 1 or 2 days. Patients with no elevated urea nitrogen or creatinine, even though renal function may be somewhat diminished, are given ordinary therapeutic doses two or three times daily.[18] Or, more precisely, when the BUN is less than 50 mg. per 100 ml. and the creatinine level is less than 2.5 mg. per 100 ml., dosages of 0.5 gm. of kanamycin at 8 hour intervals may be prescribed for 24 to 72 hours, following which the dose should be reduced to 0.5 gm. every 12 hours. When the BUN is above 50 mg. per 100 ml., or the creatinine is greater than 2.5 mg. per 100 ml., or both, the dose might well be reduced to 0.5 to 1.0 gm. every 24 hours. When the BUN exceeds 100 mg. per 100 ml. and the creatinine exceeds 5 mg. per 100 ml., 0.5 gm. ought to be given every 48 to 96 hours. In patients undergoing hemodialysis, levels of kanamycin become reduced by half in 6 to 8 hours. This procedure thus adds another variable to proper dosage of kanamycin[22] (Table 2).

Orme and Cutler also have studied the problem well.[5, 21] They observed that reabsorption of kanamycin in tubules was rather complete,

Table 2. *Serum Levels of Kanamycin (micrograms per ml.) in Anuric Patients**

| | HOURS AFTER 0.5 GM. INTRAMUSCULAR DOSE | | | | | | | |
	1	2	4	8	12	24	48	72
No hemodialysis	28	28	25	24	24	20	18	15
With 8 hour hemodialysis	25	24	19	12	–	10	7	5

*After Ory.[22]

but this did not eliminate the possibility of some tubular secretion. In any event, kanamycin clearance is directly proportional to the glomerular filtration rate at all levels of kidney function. Thus, serum half-life of kanamycin can be approximated from the creatinine clearance and body weight. They point out, for example, that a dose of 7 mg. of kanamycin per kg. per day can be repeated at intervals of 3 half-lives in hours and this should permit adequate antimicrobial therapy without dangerous accumulation of the drug that might lead to ototoxicity. This is achieved by multiplying the serum creatinine concentration (mg. per ml.) (which approximates the half-life of kanamycin in hours) by 3.

To summarize: In the adult with reduced creatinine clearance, greatly prolonged and high blood levels result and the height and extension of these are related to the degree of reduced kidney function. With this situation of high levels persisting for too long, deafness uniformly can be expected, earlier than desired. Therefore, the dosage schedule in patients with renal disease must be altered to fit the degree of dysfunction.

Infants less than 3 months old should be given lesser amounts of kanamycin. Mean half-life serum of the drug in infants is more than 13 hours, in contrast to the half-life in adults of 4 to 6 hours.[11] Doses then should be reduced from 10 or 15 mg. per kg. to 5 mg. per kg. every 12 hours.[8, 13, 26, 29] Given the appropriate indications, kanamycin can be given to infants in this amount, without overt fear of the ototoxic effects often seen in adults. Yow has summarized the pediatric experiences in this regard with these comments: "The risk of ototoxicity employing 15 mg. per kg. per day for short courses of therapy (6 to 10 days) is negligible."[29] Thus, if only 5 mg. per kg. per day is prescribed, the ototoxic effects are rare, and such a dose is sufficient for therapy of most infectious problems.

The major deterrent to the use of kanamycin is the production of deafness—paralysis of the eighth cranial nerve. Kanamycin, like other amino sugars, has a very real effect upon the functions of the organ of Corti. The toxic effects of the drug upon the integrity of the reticular membranes of this organ have been studied by many investigators.[12, 28] The organ of Corti—which receives sound waves and interprets them for sound discrimination by the brain—is a highly differentiated organ; it is fragile and easily injured. The aminoglycosides disrupt the delicate association among the variegated cells lining the organ. Although the body makes a very real effort at repairing drug-damaged hair cells and does a reputable job if the poison is not given for too long a time, or if its concentration in the organ is not too high, there is a point when it becomes totally destroyed and deafness results. This is direct tissue toxicity from the overuse of kanamycin. It is a predictable consequence and can be prevented by judicious prescription. Knowledge of kidney function and of the prolongation of serum concentrations of kanamycin in various stages of that function, and varying the length of time kanamycin is prescribed are the only ways to prevent this serious side effect (Table 3).

Table 3. *Suggestions for Avoiding Toxicity With Kanamycin**

1. Use no more than 15 mg. of kanamycin per kg. per day—less if possible (5 to 10 mg. per kg.).
2. Alter regimen in patients with poor renal function (see text). Renal functions should be measured periodically throughout therapeutic program.
3. Extend therapy for as short a period as possible (7 to 10 days).
4. Question patient frequently for presence of tinnitus. Mandatory to stop therapy upon its first appearance.
5. Audiograms needed before start of therapy. If drug is to be used for more than 7 days, repeat every fourth to seventh day. Stop drug at first indication of high-frequency loss.
6. Avoid concurrent use of other ototoxic drugs—streptomycin, gentamicin.
7. Keep patients well hydrated.

*After Finland and Finegold.[27]

EMERGENCE OF BACTERIA RESISTANT TO KANAMYCIN

As is true with many other antimicrobial agents, kanamycin's prescription for control of growth of susceptible microbes is often followed by the later emergence of some strains which demonstrate resistance to its earlier poisonous effects. There are two, perhaps different, events which occur. The first concerns the parallelism between use of kanamycin in a hospital society and the appearance of strains of organisms, initially sensitive to the drug, but later resistant. This becomes more of an epidemiological phenomenon than a deterrent to its use in a patient with infecting microbes proved to be susceptible in vitro.

For example, Dans and his colleagues have reported classical changes in the resistance patterns of Klebsiella-enterobacters in the Boston City Hospital.[6] They measured both the serotypes and susceptibilities of all isolations of these organisms in 1967, and compared them with those observed in 1963-64. They reported that there were only minor differences among the serotypes recovered in the two periods—type 24 was most frequent, type 2 was second most common, and type 26 was third. Susceptibility patterns to 10 antimicrobial agents were tested in the two periods. Kanamycin was much more widely used in the later time. There was a drop in the numbers initially sensitive on isolation to Kanamycin between 1964 and 1967 from a 90 per cent figure to 67 per cent. It is suggested, properly, that there was a notable "association between the extent of drug usage and emergence of antibiotic resistant bacterial populations."[6] Because gentamicin had been used sparingly in the two eras, there was essentially no change in the patterns of susceptibility to this agent.

The same observations have been reported concerning staphylococci—there are now seen substantially more strains resistant to kanamycin than was true 10 years ago.[11] The drop in the numbers of strains resistant to kanamycin is not a fearful exhibition yet, for the vast majority of strains of Klebsiella, E. coli, most species of Proteus, Salmonella, and Shigella are still sensitive. When the organism is proved susceptible, kanamycin continues to be a major drug to be given to a patient with a severe infection caused by any one of these.

Explanations for this resistance are not within the scope of this review. The suggestion remains, though, that any chemotherapeutic agent must be administered only when the good that it can give the patient definitely exceeds the harm that its use might give the patient — and his society.

There is a second phenomenon of resistance that is of concern. It has been noted by many that certain strains of gram-negative bacteria develop multiple drug resistances even though exposure to any single drug may not have occurred.[1] The multiple resistance phenomenon does not occur in a series of discrete steps following exposure to each of many drugs. Rather, it happens rather abruptly: a strain of microbes is noted suddenly to be resistant to a number of agents despite exposure to only one of them. It has been shown that an organism is capable of transfering its multiple drug resistances en bloc to a neighboring strain of the same or another species. To achieve this, there must be intimate contact between the two strains or species, one with resistance, the other recipient susceptible. The genetic elements controlling multiple drug resistance transfers have been designated R factors. With contact (in vitro and in vivo), the conjugation between drug-resistant donor cells and sensitive recipient cells results in multiple drug resistance in both groups.

This has been shown to occur with kanamycin. Although the phenomenon has not yet attained alarming proportions in clinical experiences, it must be speculated that resistance to kanamycin might occur with increasing frequency despite reduced usage of the drug. The capacity of one resistant strain to transfer its multiple drug resistances to another, literally virginal organism has fearful connotations. It again is the responsibility of the prescribing physician to remind himself that the administration of any antimicrobial agent to a human may result in resistance developing to that drug and, by transfer of its R factors, to other agents as well.

INDICATIONS: GENERAL

The manufacturer of kanamycin in its official package circular has described accurately that it is active against most strains of Staphylococci — albus and aureus — and E. coli, Klebsiella-enterobacters, Shigella, Salmonella, most species of Proteus, and Neisseria.[2,9] No cross-resistance between kanamycin and chloramphenicol, erythromycin, novobiocin, oleandomycin, streptomycin, penicillin, or tetracycline has been described among Staphylococcal strains. Contrariwise, there is complete cross resistance between kanamycin and neomycin, and probably to gentamicin also.[7] Kanamycin's antimicrobial spectrum is not all-inclusive. It does not inhibit most strains of Pseudomonas aeruginosa and is less effective a killing agent than other drugs against all strains of streptococci, including enterococci, and pneumococci and clostridia. Infections caused by these agents should not be treated with kanamycin.

The official package circular[2] also describes its favorable use in the following infections caused by susceptible pathogens: tracheitis, pneumonia, bronchitis, lung abscess, pleuritis, infections of skin and soft tissues, and postsurgical wound infections, in osteomyelitis, intestinal amebiasis, gastroenteritis, enterocolitis, and sepsis.

Surgical infections caused by susceptible organisms respond well to kanamycin, if the drug therapy is coupled with appropriate surgical procedures.[25] Thus the drug is supportive only. Drainage of abscesses, removal of foreign bodies, debridement of necrotic tissue, closure of perforations, and relief of obstructions cannot be avoided if the patient is to recover. Kanamycin kills pathogens—it does no more. Because sensitive gram-negative bacteria are increasingly more frequent in our society as causative agents in all kinds of surgical diseases, kanamycin becomes all the more valuable an adjunct to surgical therapy.

Urinary tract infections can be treated with kanamycin, particularly those which have proved refractory to other chemotherapeutic measures.[23] For wisest prescription in urological practice, the physician must have a plan carefully worked out and an appropriate aim as to what can be expected from the drug.[20, 23] Patients with genitourinary diseases can be grouped—those with a primary acute infection, those with asymptomatic but persisting bacteriuria, and those with a mechanically complicated urinary system. In the first group, cure can be anticipated with a good drug prescription and almost all agents are effective. In acute exacerbations of infectious problems in the other groups, kanamycin given for short courses of 7 to 10 days can be expected to alleviate the episode impressively. It often does not cure, though, and relapses, either with the original pathogen or a new species, can be predicted.[20, 23] Because of its ototoxicity and irritating effects on the kidney, repeat courses of therapy for these relapses must be given with caution. Eventually, either resistant microbes will appear or the cumulative action of kanamycin given in repeated courses will become dangerous. In the third group, not only are recurrent acute infections expected, but surgical repairs are often indicated. Again, kanamycin can be prescribed for a major intercurrent problem but cannot be expected to be useful over the long period of disability.

Patients suffering from a severe gram-negative bacillary infection can be prevented not infrequently from developing fatal septic shock with the prompt institution of a correct antimicrobial agent: "Endotoxic shock is better prevented than cured."[20] In this situation, kanamycin deservedly has a secure place, as a crucial part of the initial therapy. This will be commented upon later.

For all other surgical specialties—otolaryngology, orthopedics, neurosurgery, gynecology, etc.—patients with serious gram-negative bacillary disease, whose organisms are susceptible to kanamycin, deserve to receive the drug as part of the needed therapies. It is good for osteomyelitis, for brain abscesses, for infectious problems in sinuses and middle ear, and for pelvic inflammatory disease. The restrictions on kanamycin's use in these areas are the same—total dose must be considered with discretion for fear of unwarranted ototoxicity.

Finally, kanamycin has a place in the therapy of tuberculosis. In some clinics in France and Japan in particular, and in certain areas in the United States, kanamycin has become an important part of the long-term therapy of chronic tuberculosis, most discernibly in patients whose organisms are resistant to streptomycin and isoniazid, and who must be retreated.[15, 17] It is not used alone — rather, the regimens generally recommended include three drugs, kanamycin with two others. Dosage is 15 mg. per kg. per day given in three or four doses, 5 days weekly, for 4 months. Presuming normal hearing and kidney function at the start of such a program, toxicity has not proved serious to those who have reported upon the programs.[15, 17] The accessory drugs used are ethionamide, PAS, ethambutol, and isoniazid. Editorially, a note of caution must be exercised in this regard. Kanamycin in doses as outlined is surely dangerous to the eighth cranial nerve, and programs using 15 mg. per kg. per day inevitably and eventually are associated with a very high rate of deafness after the third week. Thus the long-term use of kanamycin in chronic tuberculosis is to be approached with great caution. But the drug does have potent antituberculous activity and can be used effectively for short periods in patients who need drug therapy other than isoniazid.

SOME SPECIFIC THERAPEUTIC SUGGESTIONS ABOUT THE USE OF KANAMYCIN

Two facts are known about kanamycin. It is a powerful killer of many microbes and it is a neurotoxic agent. Its toxicity is directly related to total dose, and the margin between efficacy and toxicity is close indeed. Some suggestions about specific usage then seem clearly indicated.

One suggestion about the use of kanamycin concerns the duration of therapy. The patient with normal renal function, and receiving standard daily doses, will virtually always develop ototoxicity if the drug is continued for long enough, with increasing incidence after the second week. As the agent generally is given for acute and severe infectious diseases, careful planning of the length of therapy should be projected from the first. In the majority of instances, a 7 to 10 day course is all that is required for maximal antimicrobial activity; thereafter, the problems of the inflammatory response in the host are far more crucial than the small number of microbes still lingering there. It is after this period that host responses have attained maximal levels and drugs are not so necessary. Using recommended daily doses, a 10 day course is safe — ototoxicity begins to occur after 15 gm. and is almost universally present after 50 gm. Obviously, a course of 7 to 10 days cannot be satisfactory for some patients, but further extension of the regimen must be the exception. When a longer program seems warranted, the physician must judge the relative merits of continued usage versus predictable toxicity.

The second suggestion about the use of kanamycin is the size of the single dose, the interval between succeeding doses, and the total

daily dose. Rarely is it necessary in the adult to administer more than 1.5 gm. daily, given in three doses of 0.5 gm. 8 hours apart. This amounts to just over 15 mg. per kg. for a 90 kg. adult. In most infections, 1 gm. daily is sufficient (or 10 mg. per kg. for a 70 kg. adult). In the child or small adult 5 to 10 mg. per kg. daily is the ideal. For example, in the 20 kg. child the top daily amount is thus 200 mg. (100 mg. every 12 hours). More does not add to the efficacy of the drug — a bug can be killed only once and its poison in a doubled amount does not kill any faster or more predictably. On occasion, when the infection is superficial, when the blood supply to the inflamed area is adequately increased, the lesser daily dose can be given safely. This would be true, for example, in a first episode of an acute lower urinary tract infection, or for an acute pneumonia occurring in an otherwise healthy lung.

Finally, there are two infectious diseases in which greater doses may be needed: a relapse of chronic osteomyelitis and in acute meningitis. In both situations there is a barrier to penetration of drug from blood to where the microbes are producing disease. In chronic osteomyelitis during a relapse, there is a major compromise to blood supply, and there is no way to improve upon this. So, more drug is required to permit effective concentrations to seep into the involved area. The blood-brain barrier is equally troublesome. Eichenwald has studied this well and what he has demonstrated in children applies to the adult. Presuming that concentrations of 10 to 12 micrograms of drug per ml. are ideal, it is evident that doses of more than 15 mg. per kg. per day are needed to achieve such in the inflamed meninges — perhaps as much as 20 mg. per kg., but surely less than 30. If this large dose is, in fact, required to save the life, its use is permitted. Cessation of therapy at the earliest possible time, though, may save the patient from deafness. This requires, of course, true clinical judgment and deftness.

SUMMARY

Kanamycin's major use is in the therapy of acute, severe gram-negative bacillary diseases, exclusive of those caused by pseudomonas and Proteus mirabilis. It has a lesser place in the management of tuberculosis, particularly in patients with isoniazid-resistant tubercle baccilli. Its use in staphylococcal disease is now almost totally stopped because of the advent of the new penicillins and cephalosporins and, as importantly, some strains of staph are now appearing which are resistant to it.[27]

Gram-negative bacillary diseases caused by E. coli, Klebsiella-enterobacter, and Proteus are relentlessly increasing in our society and in serious infections they do not respond well to therapy with streptomycin, the tetracyclines, or chloramphenicol. Thus, in both adults and infants with severe infectious problems, including the newborn, kanamycin is a drug of first choice. Only gentamicin may be considered as useful as kanamycin in these diseases when one of these organisms is the cause. This is so also when exact etiologic diagnosis is difficult

Table 4. *Indications for Prescription of Kanamycin**

1. Severe infections caused by an organism known or proved to be susceptible.
2. Severe infections caused by a presumably susceptible organism but before its identification in the laboratory.
3. Morbid infections of unknown cause or location and when laboratory identification cannot be awaited. In this instance, kanamycin should be combined with oxacillin or a cephalosporin.

*After Bunn.[3]

to make on clinical grounds alone, when one of these organisms is likely to be the offender, and when prompt, specific and effective treatment is essential before the laboratory can produce results. Kanamycin is rapidly bacteriocidal and is effective against most of the gram-negative infecting bacteria. It is the author's recommendation still that the indications listed in Table 4 are appropriately sensible.

Because of its toxicity, kanamycin clearly should not be prescribed for less serious disease and in one in which a broad spectrum bacteriostatic agent has been shown to work.

Of most crucial benefit to the very ill patient is the prescription of kanamycin as a partner in a crash antimicrobial program when results of laboratory isolations and pathogen identification cannot be awaited. In such instances, and they are not infrequent, kanamycin (or gentamicin) together with a penicillin (for control of gram-positive organisms) plus perhaps a potent antistaphylococcal agent (like oxacillin) would kill virtually any bacteria capable of causing acute disease in man. The regimen need be altered only when the laboratory results are available for interpretations. This is a very real recommendation and can be life-saving.

Kanamycin is a worthy member of our antimicrobial family. When used wisely, with caution and judgment, it will salvage man from some of his pestilences. It should not be used when a safer agent can be given and it should not be administered for long periods unless deafness can be tolerated as an unwanted side effect, as would be true if death were the alternative to ineffective therapy.

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The Polymyxins

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The polymyxins, like the tyrothricins, bacitracins, and sub-tilin, are antibiotic polypeptide products of bacteria; namely, Bacillus sp. They were discovered essentially simultaneously but quite inde-pendently in 1947 and 1948 as polymyxins in two laboratories in the United States,[3, 15] and as aerosporins in one laboratory in Great Britain.[1, 5] Through international conference, the congenerity of polymyxins and aerosporins was established and a nomenclature was adopted that recognized polymyxins A, B, C, D, and E.[3] The circulins, also anti-biotic polypeptide products of bacteria (Bacillus circulans), were dis-covered in 1949;[10] while they are not of therapeutic interest, the circulins are remarkable because of complete cross-resistance and cross-suscep-tibility with the polymyxins. Polymyxin M was discovered in 1960[6] and is probably identical with polymyxin A.[18] The status of colistin, reported as a new agent in 1952,[7] was clarified when it was shown to be polymyxin E;[16, 17] abiding by the convention that accords prece-dence to the first name given to a compound, polymyxin E will be used in the remainder of this discussion.

All the polymyxins are branched cyclic decapeptides that are cationic and appear to be antibiotic through surfactant activity.[11] They are not qualitatively distinct one from another, either in antimicrobial spectrum or in expression of toxicity. All polymyxins exhibit: (1) no clinically useful activity against gram-positive bacteria; (2) definite but clinically insignificant antifungal activity; (3) selective activity against gram-negative bacilli: Pseudomonas aeruginosa, Escherichia coli, Klebsiella sp., Enterobacter sp., Salmonella sp., Shigella sp., Vibrio sp., Pasteurella sp., Hemophilus sp., and Bordetella sp. are susceptible; Proteus sp. and Providencia sp. are solidly resistant, as are most isolates of Serratia

sp., Brucella sp., and Neisseria sp. While not rigidly applicable, it appears that the probability of susceptibility to the polymyxins increases directly with the phospholipid content of the cell wall-membrane complex. Thus, the virtually uniform susceptibility of clinical isolates of P. aeruginosa to the polymyxins correlates with the known high phospholipid content of these bacteria.[12]

Toxic reactions in man can be similarly rationalized. Interaction with the lipid-rich neurons is evidenced by paresthesias, formication, vertigo, dizziness, ataxia, weakness, visual disturbances, confusion, drowsiness, and dysphonia. While renal tubular cell membranes are not known to be especially rich in phospholipids, reabsorption of water from the glomerular filtrate so raises the concentration of filtered polymyxins — the drugs are neither secreted nor reabsorbed by the tubules — that direct injury to the cell membranes of tubular epithelial cells may result.

There is significant variation in potential for nephrotoxicity among the polymyxins: polymyxins B and E are clearly less nephrotoxic than polymyxins A (M), C, or D. It is for this reason that only polymyxins B and E have attained to therapeutic use.[1] Indeed, polymyxin B was the only polymyxin commercially available for therapy until polymyxin E — new in name as colistin — became available in 1962. On the basis of a careful molecule-for-molecule assessment, polymyxin B is significantly more active against P. aeruginosa than polymyxin E; it is also more toxic to mice — relationships that hold for the free base forms of these antibiotics as well as for sulfomethyl (methanesulfonate) derivatives.[13]

CLINICAL PHARMACOLOGY

In clinical use, the pharmacodynamics of polymyxins B and E differ materially because of the different chemical forms that are exhibited in therapy. Polymyxin B is uniformly applied as the sulfate — a simple salt that provides the free base in fully active form immediately upon administration. Polymyxin E is available as the sulfate only for peroral administration; for parenteral administration it is prepared only as a sulfomethyl derivative that is put up with dibucaine.

Neither polymyxin B nor E is absorbed in appreciable quantity from the intact gastrointestinal tract of the adult. Both are sufficiently well absorbed from the gut of the premature or newborn infant to be hazardous. Although some of the gram-negative bacillary elements of the enteric bacterial flora are suppressed by orally administered polymyxins, the ecologic dislocation is not severe and ordinarily is not cause for disease.

Absorption is also poor on topical application to the conjunctiva, paranasal sinuses, tracheobronchial tree, burns, and other wounds. However, absorption is quite prompt from serous cavities, for example, the peritoneal cavity; apnea has been provoked by intraperitoneal installation of polymyxins as sulfates.

Polymyxin B Sulfate

Intramuscular injection of polymyxin B sulfate leads to maximum concentrations in the blood in about 2 hours—a lag period that is eliminated by intravenous injection. With usual doses, concentrations of 5 to 8 micrograms per ml. of blood are attained, levels inhibitory to about 95 per cent of the clinical isolates of P. aeruginosa. The rate of decline in concentration is slow, so that administration every 8 to 12 hours is practical.

Data regarding distribution are meager. It is certain that polymyxin B fails to penetrate into the central nervous system and the eye, judging from its absence from either cerebrospinal fluid or aqueous humor even when there is inflammation of these organs. Since the drug is absorbed from serous cavities, there should be penetration into serous fluids after parenteral injection.

Renal excretion is the major route of elimination; 60 per cent of the injected dose of polymyxin B can be accounted for in the urine. Although the antibiotic appears promptly in the blood after intramuscular injection, a delay of 12 hours may intervene before urinary excretion is evident. As treatment is continued with usual doses, the urine concentration varies from 20 to 100 micrograms per ml. Polymyxin B is found in the urine for 2 to 3 days after injection has been discontinued.

Polymyxin E Sulfomethyl Derivative

Sulfomethylation obliterates the cationic nature of polymyxin E, actually converting the drug into an anionic substance. This is a drastic alteration. The fully sulfomethylated drug is not antibiotic; both the antibacterial potency and the toxicity for mammals vary directly with the degree of completeness of sulfomethylation (Fig. 1). It appears that the degree of completeness of the reaction is variable, so that a melange of molecules usually results, as can be demonstrated by subjecting sulfomethyl preparations to electrophoresis.[2] Therapeutic effectiveness actually depends on hydrolysis of sulfomethyl polymyxin E to release the active, free base. At physiologic pH in aqueous systems at body temperature, hydrolysis does occur—at a rate that is uncertain.[2] In a sense, the sulfomethylate is a repository form of polymyxin E.

Absorption after intramuscular injection is reasonably prompt, with maximum blood concentrations attained in 1 to 2 hours, followed by decline to low levels 8 to 12 hours after injection. Recommended doses yield 5 to 8 micrograms per ml. of blood, levels which are inhibitory to about 75 per cent of the clinical isolates of P. aeruginosa. The drug should not be given by intravenous injection because of the dibucaine present in the trade preparation. The pattern of distribution of polymyxin E, free base, in the body is apparently the same as that for polymyxin B. After injection as the sulfomethylate, polymyxin E usually appears in the urine within 2 hours, attaining concentrations 10 to 20 times greater than the average concentration in the blood.

The difference in the rapidity of appearance in the urine, contrasting polymyxin B injected as the sulfate with polymyxin E injected as a
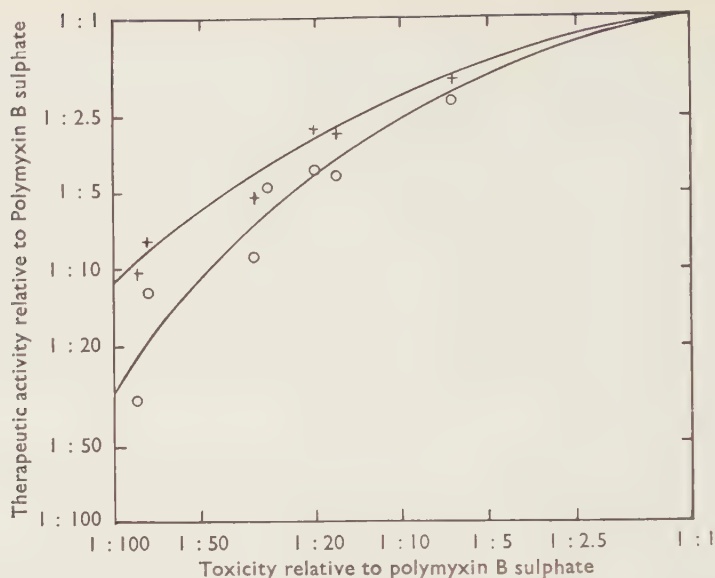
Figure 1. As the degree of sulfomethylation approaches completeness, both mammalian toxicity (abscissa; acute, intravenous LD_{50} in mice) and therapeutic efficacy (ordinate; circle = acute infection in mice with Escherichia coli; crosses = chronic infection in mice with Bordetella pertussis) decrease. Reproduced with permission from Barnett, M., Bushby, S. R. M., and Wilkinson, S.: Brit. J. Pharm., 23:552, 1964.

sulfomethyl derivative, merits consideration. In early studies carried out with the sulfates of polymyxins B and E, the rates of renal excretion were identical.[1] Sulfomethylation of polymyxin E, in converting the drug to a positively charged form, apparently facilitates renal excretion. Liberation of active polymyxin E as a consequence of spontaneous hydrolysis of the sulfomethyl derivative would proceed during formation and storage of the urine in the bladder.

PREPARATIONS AND DOSAGE

Polymyxin B Sulfate

Sterile powder is supplied in multiple dose vials containing 500,000 units (50 mg. free base equivalent). For parenteral injection, the usual daily dose is 2.5 to 3.0 mg. per kg. body weight if renal function is normal (creatinine clearance > 80 per cent of normal). If there is abnormal renal function, 2.5 mg. per kg. body weight should be injected during the first day of treatment. Thereafter, the dose must be reduced to avoid symptoms of neurotoxicity and to avoid polymyxin-induced renal injury (see Table 1). For intramuscular injection, the sterile powder should be dissolved in 2 per cent procaine hydrochloride. For intravenous injection, half the day's dose should be dissolved in 200 to 500 ml. of 5 per cent glucose solution and given over a period of 1 to 2 hours every 12 hours.

Table 1. *Reduction in Polymyxin Dosage to Avoid Drug-Induced Renal Injury*

| | PARENTERAL DOSE (MG. PER KG. BODY WEIGHT) | | | |
| | WHEN CREATININE CLEARANCE IS | | | |
	Normal, or ≥ 80% of normal	< 80% to > 30% of normal	< 25% of normal; BUN ≥ 100 mg. per 100 ml.	WITH ANURIA	EFFECT OF DIALYSIS
Polymyxin B, sulfate	2.5 to 3.0 mg. per day	1st day: 2.5 mg. Daily thereafter: 1.0 to 1.5 mg.	1st day: 2.5 mg. Every 2 to 3 days thereafter: 1.0 to 1.5 mg.	1st day: 2.5 mg. Every 5 to 7 days thereafter: 1.0 mg.	Not appreciable
Polymyxin E, sulfomethyl	3.0 to 5.0 mg. per day	1st day: 3.0 mg. Daily thereafter: 1.5 to 2.5 mg.	1st day: 3.0 mg. Every 2 to 3 days thereafter: 1.5 to 2.5 mg.	1st day: 2.5 mg. Every 5 to 7 days thereafter: 1.5 mg.	Not appreciable

For intrathecal injection, the sterile powder should be dissolved in sterile 0.9 per cent sodium chloride solution to give 5 mg. per ml. The dose is 2 to 5 mg. for children and 5 to 10 mg. for adults—given daily for the first three to four days of treatment, and every other day to completion of therapy.

Topical application to the eye, sinus tracts, or wounds (as wet dressings) involves use of solutions containing 0.5 to 3 mg. per ml. in sterile 0.9 per cent sodium chloride solution. Generally, the total amount of polymyxin B should not exceed 200 mg. per day when applied topically. However, continuous subpalpebral lavage has been employed, using a solution containing 0.5 mg. per ml.

Tablets containing 250,000 and 500,000 units (25 mg. and 50 mg. free base equivalent) are available for oral administration. The usual peroral dose is 15 to 20 mg. per kg. body weight per day, given as three equal portions, every 8 hours. Oral administration is contraindicated in premature infants and neonates.

Otic solutions containing 1 mg. polymyxin B per ml. (in propylene glycol with 1 per cent acetic acid) can be applied as drops three or four times per day. An ophthalmic ointment with 2 mg. polymyxin B per gm. is available; in addition, polymyxin B (1 mg. per gm.) is mixed with bacitracin (13 mg. per gm.); or polymyxin B (0.5 mg. per gm.) is mixed with bacitracin (10.4 mg. per gm.) and neomycin (3.5 mg. base per gm.). The ophthalmic preparations can be applied two to four times per day.

Urinary bladder irrigant solution contains 200,000 units (20 mg. free base equivalent) of polymyxin B and 40 mg. (free base equivalent) of neomycin per ml. When 1 ml. is added to 1000 ml. of sterile 0.9 per cent sodium chloride solution, a preparation suitable for continuous irrigation of the urinary bladder is obtained.

Polymyxin E Sulfate

Polymyxin E sulfate is available as a dry powder containing 300 mg. free base equivalent per bottle; suspension in water as directed yields 25 mg. per 5 ml. The usual dose is 3 to 5 mg. per kg. body weight per day by mouth, in three equal portions given every 8 hours.

Polymyxin E Sulfomethyl Derivative

Each multidose vial contains: 150 mg. base equivalent of polymyxin E as the sodium salt of the sulfomethyl derivative; 5 mg. of dibucaine hydrochloride; citric acid-sodium citrate (15 mg. and 50 mg., respectively); and 0.2 mg. thiomerosal. The recommended dose is 3.0 to 5.0 mg. per kg. body weight per day, given in two or three equal portions by intramuscular injection. Note: this preparation should not be injected intravenously, intrathecally, or intraocularly; it should not be applied to large wounds, burns, or extensively denuded body surfaces. For effectiveness against Pseudomonas aeruginosa the higher dose should be used if renal function is normal (creatinine clearance ≧ 80 per cent of normal). If renal function is abnormal, therapy should commence with administration of at least 3.0 mg. per kg. body weight during the first 24 hours of treatment. Thereafter, the dose needed to replenish

the excreted antibiotic can be estimated by questioning the patient for symptoms of neurotoxicity and by following parameters of renal function (see Table 1).

ADVERSE REACTIONS

Hypersensitivity reactions to the polymyxins are quite uncommon when these agents are used topically or orally. After parenteral injection, skin rashes (macular or urticarial) and fever may occur but are unusual. Repeated application of the ophthalmic ointment may lead to a low-grade conjunctivitis that is probably consequent of direct irritation and not sensitization.

The pain from intramuscular injection and the signs of meningismus that may follow intrathecal administration of the polymyxins as sulfates are also manifestations of the direct irritative properties of the free base, active forms of these antibiotics. Such irritative effects can be mitigated by reducing the concentration of the preparations used. There is, moreover, marked individual variation in the severity of pain felt on intramuscular injection. In one study, 6 of 21 patients given polymyxin B sulfate by intramuscular injection complained of pain at the site of injection; in one patient the intramuscular route of injection had to be abandoned because of pain.[14]

The probability of occurrence of neurotoxicity is directly related to the concentration of the free base, active form of the polymyxins that is achieved in the blood. Thus, in adults when the concentration of polymyxin B greatly exceeds 5 micrograms per ml. of blood, paresthesias (circumoral, acral), dizziness, ataxia, weakness, confusion, or drowsiness are likely to occur. These adverse reactions are seldom encountered in children; in adults there is frequently accommodation with repeated doses.

Nephrotoxicity centers around injury to the convoluted tubules. Cylindruria, proteinuria, pyuria, hematuria, azotemia, oliguria, and acute renal failure make up a progression of increasing seriousness of renal toxicity. Generally, the injury is reversible if treatment is stopped (as it should be with oliguria), or the dose is reduced (as it should be with azotemia).

THERAPEUTIC INDICATIONS AND RESULTS OF THERAPY

The polymyxins remain the agents of first choice for the treatment of infections caused by P. aeruginosa. Natively resistant strains are virtually never isolated from clinical specimens. Resistance during treatment has not been documented.

While most clinical isolates of E. coli are susceptible to the polymyxins, other agents with lesser predilection for adverse reactions should be used. However, the polymyxins are sometimes the only antimicrobics with a high probability of effectiveness—a situation much more common with Klebsiella sp. and Enterobacter sp. than it is with

E. coli. Other antibacterial agents are almost always preferable for the treatment of infections caused by Hemophilus sp., Bordetella sp., Shigella sp., and Salmonella sp., although clinical isolates of these genera are frequently susceptible to the polymyxins by in vitro testing.

Urinary tract infections probably represent the most common clinical situations in which treatment with polymyxins is undertaken. When there is no obstructive uropathy, either mechanical or patho-physiologic, the results are excellent. Pre-existing renal disease that is complicated by infection does not contraindicate the use of poly-myxins. For example, 14 patients who were treated with polymyxin B had blood urea nitrogen levels of ≥ 25. mg. per 100 ml. before therapy; in three patients there was a decrease during treatment, and in only two was there an increase. Frequently, there was a decrease in pyuria and cylindruria in course of treatment.[14]

Other organ-system localizations of infections, and generalized infections with bacteremia that are caused by bacteria that are suscep-tible to the polymyxins, particularly those caused by P. aeruginosa, are sometimes indications for treatment with these agents. Meningitis caused by P. aeruginosa requires intrathecal injection of the sulfate form of a polymyxin, such as polymyxin B sulfate. Obstructive uropathy and abscesses are not favorably affected, even when the causative bacteria are susceptible to the polymyxins.

The author's preference for use of polymyxin B rather than poly-myxin E whenever systemic therapy with a polymyxin is necessary is based on: (1) the fact of complete cross-susceptibility and cross-resistance; (2) the lesser antibacterial potency of polymyxin E; (3) the limitation imposed on the clinical utility of polymyxin E by chemical conversion to a sulfomethyl derivative – sulfomethyl polymyxin E should not be given by intravenous, intrathecal, or intraocular injection or used topically; (4) the lesser cost of polymyxin B.

Oral administration of the polymyxins is possibly effective in the treatment of shigellosis, although other agents, such as ampicillin, appear to be preferable.

Topical administration, using either polymyxin B or E as the sulfate, by continuous, subpalpebral lavage, has been successfully applied in the treatment of keratitis caused by P. aeruginosa. In combination with other antimicrobics, such as neomycin, the polymyxins have also been of value in treatment of purulent conjunctivitis caused by suscep-tible bacteria, and in otitis externa when there is a significant bacterial component to the disease. Prophylaxis of urinary tract infections when short-term indwelling urethral catheterization is necessary is another situation of proved good effect from local application.

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Colistin and Sodium Colistimethate

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Colistin, a basic polypeptide antibiotic isolated from Japanese soil,[19] is a fermentation product of Bacillus polymyxa var. colistinus. The drug has been in clinical use in the United States since 1959, and for several years longer abroad. It possesses bactericidal activity against most gram-negative bacilli, and has particular therapeutic value in infections due to Pseudomonas aeruginosa. Although originally thought to be a new antibiotic, subsequent studies have shown it to be identical with polymyxin E,[30, 41] which had not been previously available for clinical use.

TERMINOLOGY. The term "colistin" has now become widely established in the world literature and continues to be used rather than polymyxin E. This usage helps to avoid confusion with polymyxin B, to which the drug is related but not identical.[42]

Additional factors have contributed to past confusion in nomenclature: (1) there are two preparations of colistin available for clinical

Table 1. *Nomenclature for Colistin Preparations*

GENERIC NAME	TRADE NAME	TERMS PREVIOUSLY USED
sodium colistimethate (only methane sulfonate derivative of the polymyxins available)	Coly-Mycin M Intramuscular[*] (for intramuscular use only)	colymycin, colistin, colistin methane sulphonate, colistimethate sodium, etc.
colistin sulfate (polymyxin E sulfate)	Coly-Mycin S Oral Suspension Coly-Mycin S Otic Coly-Mycin S Ophthalmic[**] (for topical use)	colymycin, colistin

[*]Contains dibucaine hydrochloride
[**]For investigational use only

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COLISTIN BASE
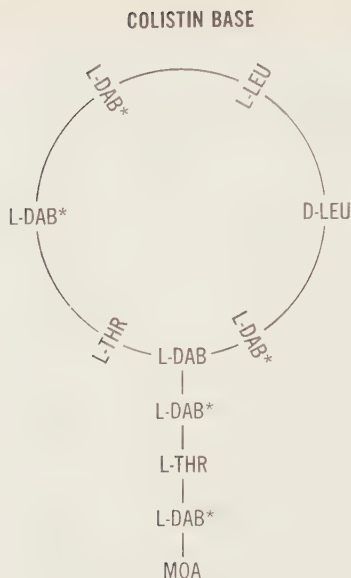
DAB REACTIVE SITE
*Substituting -CH$_2$-SO$_3^-$
at these points makes the
compound colistimethate.

$$H-\overset{\overset{\text{C}===\text{O}}{|}}{\underset{\underset{\alpha\ \ \text{NH}}{|}}{\text{C}}}-CH_2-CH_2-\overset{\overset{\text{H}}{|}}{\text{N}}-CH_2-SO_3$$

α NH γ
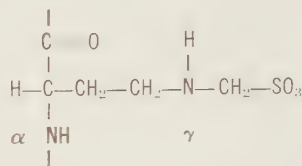
L-DAB: L-α, γ-diaminobutyric acid (*these
five have the terminal γ-amino group avail-
able for methanesulfonation)

L- or D-LEU: L- or D- leucine

L-THR: L-threonine

MOA: 6-methyloctanoic acid (or iso-octanoic
acid)

Figure 1.   Abbreviated structures of colistin base and sodium colistimethate.

use, colistin sulfate and sodium colistimethate, and (2) both these preparations have been used parenterally abroad under the designation "colymycin" or "colistin."

The currently approved nomenclature for the two colistin preparations, as well as the previously used terms, are summarized in Table 1. The official generic or trade names should be used in prescribing these drugs or reporting on their use, in order to avoid confusion.

CHEMICAL PROPERTIES.   Colistin base has a molecular weight of approximately 1170. The abbreviated chemical structures for colistin base and sodium colistimethate are shown in Figure 1. Sodium colistimethate, the derivative, is formed by the reaction of the diaminobutyric acid free amino groups of the parent antibiotic with formaldehyde and sodium bisulfite.

PHYSICAL PROPERTIES.   Colistin sulfate and sodium colistimethate are heat-stable and water-soluble. They precipitate from aqueous solutions at pH levels above 7.5 and 9.0, respectively. In dry form they are stable at room temperature for approximately 18 months.[26] In aqueous solutions, stability varies with the preparation.

CLINICAL PHARMACOLOGY

Colistin sulfate and sodium colistimethate are both rapidly absorbed after intramuscular injection. They differ, however, in the following

ways: (1) sodium colistimethate has a markedly decreased toxicity compared with colistin sulfate in both animals and man; (2) sodium colistimethate has approximately one-third the in vitro antibacterial potency of colistin sulfate; (3) sodium colistimethate is less painful on intramuscular injection; and (4) the sulphomethyl derivative is excreted in the urine to a high degree whereas colistin sulfate is not, the urine/plasma ratios being 10 to 20/1 and 2 to 3/1, respectively.[34, 10] Because of its greater toxicity, colistin sulfate is limited to topical use, while sodium colistimethate is indicated for systemic therapy. The differences in urinary excretion of the two drugs might explain the greater toxicity of colistin sulfate. The antibacterial spectra of colistin sulfate and sodium colistimethate are the same.

Maximum serum levels of sodium colistimethate are usually reached 1 to 2 hours following a single intramuscular injection. The serum level decreases rapidly in the next 4 to 6 hours (serum half-life, 4.5 hours),[13] and more slowly thereafter. Following a single intramuscular dose of sodium colistimethate, the serum level varies proportionately with the dose administered.[11] After repeated doses of sodium colistimethate, blood levels tend to rise above those predicted after single doses.[3] Administration of 150 mg. of sodium colistimethate intramuscularly yields serum levels of 2 to 8 micrograms per ml. (range of minimal inhibitory concentration for most sensitive organisms) with detectable activity up to 24 hours.[44]

While the metabolic fate of colistin base is unknown, studies by Beveridge and Martin[2] suggest that hydrolysis of the sodium colistimethate derivative occurs in both simple aqueous and biological systems, with an increase in antibacterial activity. It has been suggested that the antibacterial activity of sodium colistimethate in man increases with the conversion of the more fully substituted sodium colistimethate derivative back toward the nonsubstituted colistin base.[1, 23]

Colistin sulfate and sodium colistimethate are very poorly absorbed from the gastrointestinal tract. It is estimated that 200 times the intramuscular dose of sodium colistimethate is required to produce comparable serum levels following oral intake.[33]

Sodium colistimethate diffusion across the blood-brain barrier is poor and unpredictable.[45]

MECHANISM OF ACTION

The mode of bactericidal action of colistin sulfate and sodium colistimethate is through surface detergent activity which damages the cytoplasmic membrane, resulting in the leakage of vital cellular contents.[25]

Colistin sulfate and sodium colistimethate are rapidly bactericidal. Chabbert[6] reported that after exposure of sensitive bacteria to concentrations of colistin sulfate just above the minimal inhibitory concentration for 80 minutes, less than 0.01 per cent of organisms survived, and antibacterial activity began within 1 to 10 minutes after contact with the organism.

ANTIBACTERIAL SPECTRUM AND SENSITIVITY

Although the greatest therapeutic value of sodium colistimethate has been in Pseudomonas infections, it is also effective in treating infections due to susceptible Klebsiella, Escherichia, Enterobacter (Aerobacter), and Hemophilus organisms.[5, 7, 10, 17, 18, 29] Proteus species are almost invariably resistant to sodium colistimethate.

The in vitro inhibitory concentration of sodium colistimethate for most organisms sensitive to the drug is between 1.6 and 5.0 micrograms per ml.[10, 28, 33] Summarized in Table 2 is the in vitro antibacterial activity of colistin sulfate and polymyxin B sulfate against common gram-negative pathogens, based on pooled data from 22 investigative groups.[33] Since the in vitro antibacterial spectra for colistin sulfate, polymyxin B sulfate, and sodium colistimethate are essentially the same, these data give a close indication of specific strain sensitivity to sodium colistimethate. The minimal inhibitory concentrations of sodium colistimethate may differ, however, from those reported in the table for colistin sulfate and polymyxin B sulfate.

Although sodium colistimethate has been in clinical use for more than 10 years, there has been no appreciable change in the in vitro susceptibility of previously sensitive organisms. Of equal importance, bacterial resistance develops with difficulty in vitro, and rarely, if at all, clinically.[18, 33, 39] There is total cross resistance with polymyxin B sulfate, but no cross resistance with other antibiotics. Resistance to sodium colistimethate has not been reported in association with resistance transfer factors.

Table 2.   *In Vitro Bacterial Sensitivity to Colistin Sulfate and Polymyxin B Sulfate*[33]

ORGANISM	NO. OF STRAINS TESTED	PER CENT OF STRAINS SENSITIVE TO LESS THAN 10 MICROGRAMS PER ML.*
Klebsiella	65	98
Hemophilus	191	96
Pseudomonas	685	95
Escherichia	1126	90
Aerobacter	64	85
Proteus	127	2

*All values were converted to base equivalents

CLINICAL ASPECTS

Since the clinical indications for the use of colistin sulfate and sodium colistimethate differ substantially, the two drugs will be discussed separately.

Sodium Colistimethate

Sodium colistimethate is one of few antibacterial agents effective in the treatment of Pseudomonas aeruginosa infections, including

septicemias, wound infections, urinary tract infections, and infections of the respiratory system.[5, 32, 46] There are numerous reports on the successful treatment of infections due to Klebsiella (including Klebsiella pneumonia), Escherichia, Aerobacter, and Hemophilus with sodium colistimethate.[10, 17, 38, 46] In general, the therapeutic efficacy of sodium colistimethate follows closely the predicted in vitro effect. The drug has been particularly useful in the treatment of gram-negative infections resistant to other antibiotics.[46] Best results have been reported in the treatment of urinary tract infections or septicemias arising therefrom, and least favorable results in the management of infections requiring high serum or tissue concentrations, such as osteomyelitis, abscesses, cholecystitis, endocarditis, and chronic pulmonary infection. The poor tissue-permeability of sodium colistimethate may be a consequence of its relatively high molecular weight.

The success of sodium colistimethate in the treatment of urinary tract infections due to sensitive organisms may relate to the easily attained high urinary concentration, approximately 50 micrograms per ml. after 75 mg. injected intramuscularly every 12 hours.[35] If the cure of urinary tract infection depends on the antibiotic concentration in the urine, as suggested in an extensive investigation,[35] then sodium colistimethate should be preferred to polymyxin B sulfate in treatment of such infections or septicemias arising therefrom (see Table 4).

DOSAGE AND ADMINISTRATION. The recommended dose of sodium colistimethate is 1.5 to 5.0 mg. per kg. per day, in two to four divided doses. The average daily dose, 2.5 mg. per kg. per day, has been adequate for most infections. Lower doses (1.5 to 2.0 mg. per kg. per day) may be adequate in urinary tract infections where a high urinary concentration is assured, while doses of 4 to 5 mg. per kg. per day are best reserved for serious infections and septicemias. The total daily dose should not exceed 5 mg. per kg. per day to avoid nephrotoxicity, the most serious adverse effect.

The currently available preparation of sodium colistimethate contains dibucaine and is intended for intramuscular use only. A preparation without dibucaine, which will be suitable for intravenous or intrathecal use, should be available soon.

DOSAGE IN RENAL INSUFFICIENCY. The dosage of sodium colistimethate requires reduction in patients with significant renal insufficiency, since the drug is excreted primarily by the kidney.[13, 22, 37] The recommendations in Table 3 are based on endogenous creatinine clearance, a more accurate index of renal function than serum urea or creatinine.

No major alteration in sodium colistimethate dosage is required during peritoneal dialysis, since the amount removed is approximately only 1 mg. per hour.[13, 14] Since measurable quantities of the drug are not recovered during hemodialysis,[12, 13] peritoneal dialysis would be the appropriate dialytic therapy for toxic overdosage.

TOXIC SIDE EFFECTS. Nephrotoxicity, the most serious potential toxic effect of sodium colistimethate, is almost invariably associated with: (1) the use of higher than recommended doses in patients with normal renal function; (2) failure to reduce dosage in patients with renal

Table 3. *Recommended Dosage of Sodium Colistimethate in Patients with Renal Insufficiency*[13]

DEGREE OF RENAL IMPAIRMENT	ENDOGENOUS CREATININE CLEARANCE (ml./min.)	PER CENT OF RECOMMENDED DAILY DOSE	DOSAGE INTERVAL
None or mild	Above 75	100	q. 12 hours
Moderate	Above 20	75–100	q. 12 hours
Severe	5–20	50	q. 12 hours
Negligible renal function	Less than 5	30–35	q. 12 to 18 hours

impairment; or (3) concomitant use with other nephrotoxic antibiotics.[8, 20, 43] Monitoring of urinary output and serum urea or creatinine can give warning of early nephrotoxicity. When the daily dose is high or renal reserve low (as in elderly patients), monitoring is of greater importance. Therapy should be discontinued at the first sign of developing renal impairment. If this is done, nephrotoxicity is reversible. After the return of normal renal function, therapy may be reinstituted at lower dosage, if indicated.

Neurotoxicity due to sodium colistimethate is of two types: (1) transient neurological symptoms such as circumoral paresthesias, numbness, and tingling, usually alleviated by a decrease in dosage; and (2) neuromuscular blockade which is rare and should not occur with proper usage. Neurotoxicity has been reported in association with overdosage, failure to reduce dosage in patients with renal insufficiency, and the concomitant use of either curariform agents such as muscle relaxants during anesthesia or antibiotics with similar neurotoxic effects (kanamycin, neomycin, streptomycin, polymyxin B sulfate).[27, 30, 43] Complaints of generalized muscle weakness or fatigue may signal the onset of neuromuscular blockade, which could progress to apnea if therapy is not promptly discontinued. Assisted respiration may be required until blood levels fall.

While there are conflicting reports on the comparative toxicity of sodium colistimethate and polymyxin B sulfate, it is generally agreed that in clinical use polymyxin B sulfate is the more toxic of the two.[29, 32, 38] In animal studies, Vinnicombe and Stamey[40] reported polymyxin B sulfate to be more nephrotoxic than sodium colistimethate. Brownlee, Bushby, and Short[1] reported polymyxin E sulfate (identical with colistin sulfate) less nephrotoxic than polymyxin B sulfate. Summarized in Table 4 are data on comparative efficacy and toxicity for the clinically available antibiotics effective in the treatment of Pseudomonas infections. Whereas the potential toxic effects of sodium colistimethate and polymyxin B sulfate are generally reversible, the ototoxicity associated with gentamicin is irreversible. Sodium colistimethate appears to offer a wider therapeutic margin of safety than either polymyxin B sulfate or gentamicin.

Table 4.　*Efficacy and Limitations of Antipseudomonas Agents*

	SODIUM COLISTIMETHATE	POLYMYXIN B SULFATE	GENTAMICIN
Efficacy against:			
Pseudomonas	+	+	+
Klebsiella	+	+	+
Escherichia	+	+	+
Aerobacter	+	+	+
Proteus		−	+
Local Pain or Irritation	Negligible	Frequent	Negligible
Antibacterial Concentration in Urine	Good	Poor	Good
Limit on duration of use	No	No	Yes
Retreatment Safe	Yes	Yes	No
Nephrotoxicity	Yes	Yes	Yes
Neurotoxicity	Yes	Yes	Unknown
Ototoxicity	No	No	Yes*

　+ Effective
　− Ineffective
　　Auditory and vestibular

Colistin Sulfate

Because of its severe toxicity when administered parenterally, colistin sulfate is approved for topical and oral use only. Two preparations are available commercially: (1) colistin sulfate for oral use (Coly-Mycin S Oral Suspension), and (2) colistin sulfate-neomycin sulfate-thonzonium bromide-hydrocortisone acetate for otic use (Coly-Mycin S Otic). A third preparation, colistin sulfate ophthalmic (Coly-Mycin S Ophthalmic), is available in this country for investigational use.

ORAL COLISTIN SULFATE THERAPY.　The oral preparation of colistin sulfate is used primarily in the treatment of bacterial diarrheas of infancy and childhood. Its greatest efficacy has been in the treatment of infections due to enteropathogenic Escherichia coli.[7, 11, 15] In vitro bacterial studies suggest that it is the most effective agent of many tested against these organisms.[15] In the event of tissue or blood stream invasion, parenteral sodium colistimethate can be used adjunctively. There have been no reports of systemic toxicity from the use of Coly-Mycin S Oral Suspension alone, since negligible quantities are absorbed from the gastrointestinal tract when given in recommended doses. Although 99 to 100 per cent of Salmonella and Shigella organisms were sensitive to 10 micrograms per ml. or less of colistin sulfate in vitro,[33] therapeutic results have been variable. With other than Escherichia infections, the use of oral colistin sulfate should generally be dictated by sensitivity studies.

The usual dosage is 3 to 5 mg. colistin base per kg. per day given in three divided doses, rarely to exceed 7.5 mg. colistin base per kg. per day. In enteropathogenic Escherichia coli epidemics, doses of 10 to 25 mg. colistin base per kg. per day were required to produce good results, and were not associated with toxicity.[11]

OTIC COLISTIN SULFATE THERAPY. The four ingredients in Coly-Mycin S Otic were chosen based on the pathologic and bacteriologic manifestations of otitis externa. Colistin sulfate and neomycin sulfate, used together, provide antibacterial activity against the three commonest organisms isolated in otitis externa, Pseudomonas, Staphylococcus, and Proteus. Thonzonium bromide, having surfactant properties, promotes penetration of the exudate by the drug to obtain tissue contact, while the hydrocortisone acetate exerts an anti-inflammatory effect. Coly-Mycin S Otic has been very effective in the treatment of otitis externa and its variant, "swimmer's ear."[9, 21, 31] Symptomatic improvement is rapid after the onset of therapy. The recommended dosage is 4 drops, 3 times daily. Its prophylactic use, 4 drops before and after swimming, is said to be effective in individuals susceptible to otitis externa.

OPHTHALMIC COLISTIN SULFATE THERAPY. In investigational use, Coly-Mycin S Ophthalmic has been effective in the management of eye infections due to Pseudomonas.[16, 21] Pooled data on its use in 165 patients by 123 investigators showed an 89 per cent satisfactory response when Pseudomonas was the causative organism, and an 83 per cent satisfactory effect for all patients.[21] Because Pseudomonas eye infections often threaten the rapid loss of vision, the ophthalmic preparation of colistin sulfate should prove an important drug in the treatment of such infections.

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Vancomycin and Novobiocin

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Vancomycin and novobiocin are two antibiotics which were developed primarily in response to the need for new agents to be used in the treatment of staphylococcal infections. A significantly large and increasing proportion of these organisms were shown to be or were becoming resistant to penicillin G, erythromycin, tetracyclines, and the other available antibiotics which, up to that time, had been employed most frequently to treat such infections. Because of the development of newer agents effective against staphylococcal infections, these antibiotics in recent years have not enjoyed their previous popularity and use. However, vancomycin, because of its uniquely potent antibacterial action, has continued to be a valuable agent in the treatment of staphylococcal infections in selected patients. Moreover, because of the inexorable sequence of events in the host-parasite-drug relationship, to be described later in this article, vancomycin may again resume its role as a very useful antistaphylococcal agent.

On the other hand, novobiocin has limited usefulness because there are several other agents now available which possess an equal degree of antimicrobial activity but without the same potential for serious untoward reactions.

VANCOMYCIN

Vancomycin is one of the most potent antibiotics available against certain bacteria. Despite certain drawbacks, it has an important place

in the treatment of serious staphylococcal infections, especially those due to strains which are resistant to other antistaphylococcal agents.

Chemical Properties

Vancomycin is produced by Streptomyces orientalis. The first culture was derived from a soil sample obtained by a missionary in the Indonesian jungles and two other strains were later isolated from samples of Indian soil.[14, 16] It was developed by the Lilly Research Laboratories. Vancomycin hydrochloride, which appears to have no significant chemical relationship to any other known antibiotic, is a white solid material and is a large molecule, having a molecular weight of approximately 3300. It is an amphoteric substance, and crystalline preparations of the free base and sulfate have been prepared. Electrophoretic studies have shown that the crystalline substance contains some 20 per cent of a second component, the biological activity of which has not been determined. It is quite soluble in water and is moderately stable in solutions at a pH between 3 and 5.[7, 8, 14]

Antimicrobial Activity and Mechanism of Action

Vancomycin is strongly bactericidal for many gram-positive bacteria, especially staphylococci. Other organisms which are usually susceptible to vancomycin include hemolytic streptococci, pneumococci, enterococci, gonococci, corynebacteria, and clostridia. It is not effective against Klebsiella, Brucella, Proteus, Shigella, Salmonella, Pseudomonas, Aerobacter, and other coliform organisms, or against Mycobacterium tuberculosis, fungi, and yeast.[18] Virtually all pathogenic staphylococci are killed by 10 micrograms per ml. or less, and the great majority are susceptible to concentrations of less than 3 micrograms per ml. Resistant mutants are rare in susceptible microbial populations. Serial subculture of staphylococci in increasing sublethal concentrations of vancomycin either produces no change in susceptibility or results in the slow, stepwise development of slight resistance. Staphylococcus aureus probably does not become resistant during the course of treatment with vancomycin.[25] There is no cross resistance with other known antibiotics.[9]

Vancomycin inhibits the utilization of disaccharide (-pentapeptide)-phospholipid, a step essential for bacterial cell-wall synthesis.[24] Its site of action is different from that of penicillin. Vancomycin inhibits mucopeptide synthesis, and uridine nucleotides accumulate in cultures of Staphylococcus aureus exposed to the antibiotic. Incorporation of specific labeled amino acids into the cell wall is also inhibited by vancomycin. Interference with the growth of spheroplasts indicates that the antibiotic may have direct effects on the bacterial membrane. It appears, however, that the primary site of action is wall mucopeptide synthesis and that membrane damage occurs secondarily to this effect.[3]

Absorption, Distribution, and Excretion

Vancomycin is not absorbed from the gastrointestinal tract; however, the orally administered drug is active within the intestinal lumen, which makes it useful in the treatment of staphylococcal enterocolitis. When administered systemically, the drug should be given intravenously

because it is quite irritating, making intramuscular injection painful. Bactericidal serum levels in humans are readily achieved and maintained by intravenous administration. After rapid intravenous infusion of 0.5 gm. in adults or 20 mg. per kg. in children, a peak plasma level of 50 micrograms per ml. at 1 hour may be demonstrated and serum levels of 10 micrograms per ml. or more may be maintained for 2 or more hours. In order to achieve such high peak concentrations, it is preferable to administer the total daily dose in two or four separate intravenous injections given rapidly.[9, 18, 21, 23]

The drug is widely distributed in tissues and body fluids. Vancomycin diffuses readily into the pleural, ascitic, and synovial fluids, but only small amounts are secreted in the bile. It does not diffuse into the spinal fluid through normal meninges, even after multiple doses, but may pass the blood-brain barrier in cases of meningitis.[4, 10, 18]

Excretion is mainly through the kidneys into the urine, more than 80 per cent of the administered drug within a 24 hour period being recovered from the urine. The half-life of vancomycin in the blood has been estimated to be approximately 6 hours.[18] In the presence of renal insufficiency, significant accumulations in the blood may develop with serious toxic potential. For anuric adult patients, a single 1.0 gm. dose may give persistent therapeutic serum levels for 10 days. Hemodialysis fails to remove vancomycin to any significant degree.[9]

Indications and Clinical Use

At the present, the only indication for the use of vancomycin is for severe infections due to pathogenic staphylococci in situations in which other drugs have failed or cannot be administered or the causative organism is susceptible only to vancomycin. In such situations it merits serious consideration. Figure 1 depicts the value of vancomycin in such a situation. This 14 year old girl with congenital heart disease and bacterial endocarditis was treated intensively with a variety of antibiotics, including antistaphylococcal agents, for a 3 week period, but blood cultures remained positive, fever persisted and clinical deterioration progressed. Institution of therapy with vancomycin produced a prompt and lasting response.

Vancomycin is not indicated for treatment of mild staphylococcal infections, because of the availability of other effective and less toxic agents, such as the penicillins, cephalothin, and erythromycin. Before the development of the semisynthetic penicillins and cephalosporins effective against pathogenic staphylococci, vancomycin was frequently employed with notable success in the management of serious staphylococcal infections.[5, 12, 19, 21] Following the introduction into clinical use of these newer agents, which are associated with fewer side effects, the use of vancomycin decreased significantly. More recently a number of staphylococcal infections due to strains resistant to methicillin as well as to beta-lactam antibiotics have been observed in Europe as well as in this country.[2, 19, 20] Vancomycin has been shown to be generally effective in the treatment of such infections after therapy with other antibiotics had failed.[2] In view of the significant geographic spread of methicillin-resistant staphylococcal infections, vancomycin may
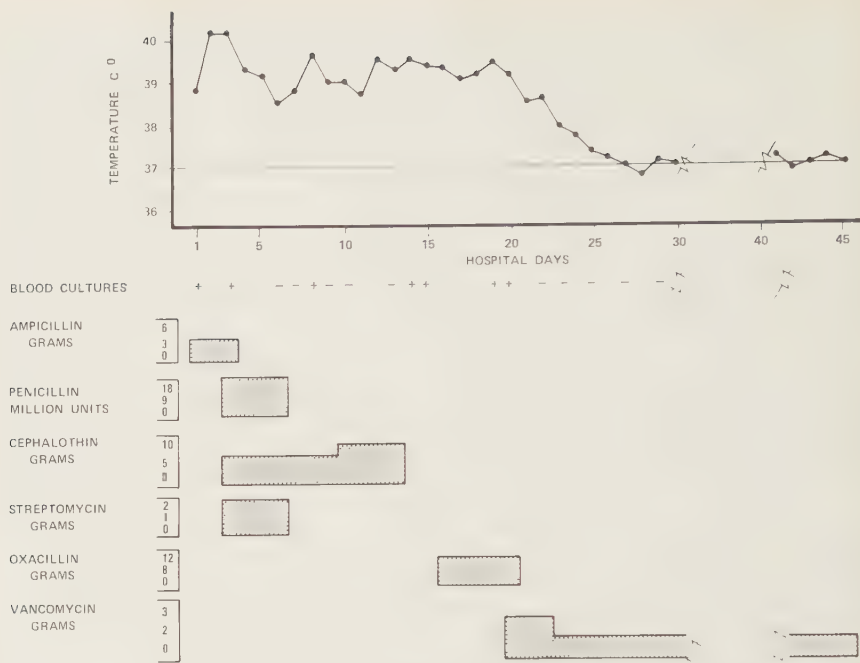
Figure 1.   Clinical and bacteriologic response to vancomycin in an adolescent girl with staphylococcal endocarditis who had failed to respond to multiple-antibiotic therapy.

again assume an increasingly important role in the treatment of such infections. Examples of serious staphylococcal infections in which vancomycin may be indicated include septicemia and other forms of sepsis, endocarditis, osteomyelitis and extensive soft tissue infections, pneumonia and its complications, and enterocolitis. The minimum length of treatment of staphylococcal endocarditis is not established with vancomycin, but it is likely that 3 to 4 weeks of treatment which achieves satisfactory bactericidal levels may be sufficient, in contrast to the 5 or 6 weeks commonly employed with other drug regimens in this infection.[9] Satisfactory results in enterococcal endocarditis have been reported.[6] In staphylococcal enterocolitis, vancomycin is given by mouth every 4 to 6 hours.

Vancomycin may be used in patients seriously ill with infections caused by other gram-positive organisms; however, infections due to streptococci and pneumococci usually respond well to more easily administered agents such as penicillin and its use in such infections is almost never indicated.

Recently, topical vancomycin has been employed successfully for the treatment of necrotizing ulcerative gingivitis and other infections of the oral cavity.[15]

Vancomycin therapy may fail if measurable bactericidal blood levels of drug are not achieved or if established abscesses or foci of sequestered organisms are present.[25]

Preparations, Administration, and Dosage

Vancomycin is marketed for intravenous use, in 10-ml. vials containing 50 mg. per ml. of solution. The drug should be administered only by the intravenous route. An intramuscular preparation has also been utilized in experimental studies (unpublished observations) but this product is not to be made commercially available. There are several methods of intravenous administration: intermittent infusion, direct injection, and continuous injection.* Intermittent infusion at 6-hour intervals is usually desirable because it provides intermittent high levels of the drug; however, the method of administration should be individualized for each patient.[18]

The usual adult dose is 2 gm. per day, and doses larger than this should be avoided except occasionally for initiating therapy in a severely ill patient with normal renal function. In children a total daily dose of 20 mg. per lb. per day divided into equal aliquots and administered intermittently at 8 or 12 hour intervals or given by continuous drip is usually satisfactory. In serious, overwhelming infection, doses as high as 68 mg. per lb. per day have been used without significant untoward effects.[18] For premature and full-term newborn infants, a dose of 6 mg. per lb. per day has proved satisfactory.[1, 18] A dose of 15 mg. per kg. per day has been recommended by others for this age group.[17] Until more experience has been accumulated, it is probably desirable to use the drug in neonates with caution and to adjust dosage on the basis of serial determinations of serum concentration. Except in very special circumstances, vancomycin should not be employed in patients who are taking or have recently been exposed to other ototoxic and nephrotoxic agents or in those with renal insufficiency.[11, 18, 25]

Toxicity

Vancomycin has a low order of toxicity in experimental mice, rats, and animals. In monkeys and dogs, daily intravenous dosage of 25 to 50 mg. per kg. per day for 3 months or longer produced no signs of toxicity.[1]

Among the hypersensitivity reactions associated with vancomycin are macular skin rashes and anaphylaxis. Phlebitis and pain at the site of intravenous injection occur but can be minimized further by using dilute solutions and alternating the sites of injection. Further purification of the agent has significantly reduced their incidence. Nausea, chills, and fever may occur and a shocklike state may develop during the course of intravenous infusion. The febrile reaction occurring with some of the earlier lots often made clinical evaluation of therapeutic response difficult.[21]

The most significant untoward reactions involve ototoxicity and nephrotoxicity. Deafness, which may be permanent, may follow the use of this drug. In some instances, hearing returns to normal after termination of therapy, but in others loss progresses despite cessation of treatment. Deafness appears to occur only in the presence of exces-

*See Riley[18] regarding technique, division of dose, and other details of administration.

sively high blood levels, i.e., 90 micrograms per ml. or greater. A transient rise in blood urea nitrogen may occur; severe renal damage with death due to uremia has been observed occasionally. Since the risk of toxic effects is appreciably increased by high serum concentrations, vancomycin should be avoided in patients with renal insufficiency. If the drug is required in such instances, renal function and auditory acuity should be monitored at frequent intervals. Significant hematopoietic disturbances and hepatic toxicity have not been a problem with the use of vancomycin. Superinfections due to gram-negative bacteria or fungi may develop during the course of vancomycin therapy.[9, 18, 20, 21, 25]

NOVOBIOCIN

Novobiocin was discovered simultaneously in 1955 in several laboratories, in each instance from the fermentation products of an apparently different and new species of Streptomyces. Streptomyces niveus was isolated by Smith and co-workers[20] and the antibacterial substance that it produced was named novobiocin. Wallick et al.[23] demonstrated that Streptomyces spheroides elaborated an antibacterial agent, which was termed streptonivicin. Both compounds appeared to have the same range of antimicrobial activity and other characteristics. Another antibiotic, cardelmycin, discovered in another laboratory, also proved to be the same as novobiocin.[7] Confusion was increased by the fact that the monosodium salt was marketed under another name and the products of two other companies were also shown to be identical. Thus, a single antibiotic had no less than six different names within a few months of its discovery. By common agreement, the antibiotic was given the generic name, novobiocin.[8]

Chemical Properties

Novobiocin is a dibasic acid. Its structure is characterized by a 9-carbon sugar attached glycosidally to a dihydroxymethyl-coumarin. The empirical formula is $C_{31}H_{36}N_2O_{11}$. It is usually supplied as the calcium or monosodium salt. Novobiocin combines with the common antibiotics in stoichiometric proportion to form salts insoluble in water; antibiotics which are neutral, acidic, or amphoteric do not form salts with it.[8] The preparation usually employed for oral administration in capsules has been the monobasic sodium salt, whereas the calcium salt, which is more stable, has been used to prepare suspensions for pediatric use.[6, 24]

Assay of the antibiotic is carried out by methods similar to those employed for other antimicrobiologic agents; a chemical assay is also available.[3]

Antibacterial Activity and Mechanism of Action

The range of antibacterial activity of novobiocin is similar to that of penicillin and erythromycin, although its action is not related to either of them. Staphylococcus aureus and pneumococci are the most

sensitive organisms, most strains being inhibited by concentrations of 1 microgram per ml. or less; some strains of staphylococci are susceptible only to 5 micrograms per ml., while about 0.5 per cent are not suppressed by concentrations as high as 25 micrograms per ml. Streptococci are relatively resistant. Group A streptococci and Strep. viridans are inhibited by 1 to 10 micrograms per ml.; Strep. viridans is particularly variable in its susceptibility. Enterococci are much less sensitive. Corynebacterium fails to grow in a concentration of 5 micrograms per ml. Hemophilus influenzae, H. pertussis, and N. meningitidis are moderately susceptible, most strains being inhibited by 10 micrograms per ml. or less. Considerable attention has been given to the action of novobiocin against Proteus. Some strains of Proteus, particularly Proteus vulgaris, are quite susceptible to novobiocin; the majority are resistant. Of other Enterobacteriaceae, most strains of Escherichia coli, Aerobacter, Klebsiella, various species of Salmonella, Shigella, and Pseudomonas require higher concentrations or are resistant to 100 or even 400 micrograms per ml. Some strains of Pasteurella are susceptible to 12.5 micrograms per ml., but those of Brucella have required 30 to 50 micrograms per ml. Most strains of Mycobacterium are not susceptible to novobiocin, but some are inhibited by high concentrations.[1, 8, 12, 24]

Novobiocin ordinarily has a bacteriostatic action but may exert bactericidal activity at high concentrations.

The exact mode of action has not been completely elucidated. Nucleotide derivatives of muramic acid, cell wall precursors, accumulate in Staphylococcus aureus treated with novobiocin, suggesting interference with cell wall synthesis,[26] but there is evidence, both biochemically and from comparative effects on L-forms, that it does not operate in the same manner as penicillin and D-cycloserine.[17] Damage to the cellular membrane is indicated by the progressive leakage of intracellular constituents, which follows exposure of Escherichia coli to the antimicrobial. Brock[1] has suggested that novobiocin induces a deficiency of magnesium in bacteria and that this leads to damage to the cell membrane and death. Novobiocin, in addition to its effect on wall synthesis and cell permeability, causes a very rapid inhibition of DNA, RNA, and protein synthesis. The mechanism by which novobiocin inhibits DNA and RNA is apparently direct inhibition of the template-polymerizing enzyme complex.[21] It also inhibits DNA polymerase, possibly through binding to the enzyme.[10]

Plasma, large inoculum size, and alkalinity decrease the antimicrobial effectiveness of the drug. The presence of 10 per cent or more serum or blood causes a marked decrease in the antibacterial activity of novobiocin. About 90 per cent of the antibiotic is bound to plasma proteins.[24] Novobiocin may displace other substances from protein binding sites, and one possible effect of this is to lower the plasma-bound iodine by displacing thyroxine.[8]

Resistance and Cross Resistance

Serial subculture of sensitive organisms in increasing concentrations of novobiocin results in the development of stepwise resistance,

rapidly at first and then more slowly.[21] Many species of bacteria, including staphylococci, initially susceptible to novobiocin, readily develop resistance to it in vitro. Substantial increase in the resistance of the infecting staphylococcus during treatment has also been observed by many investigators.[8]

The combined action of novobiocin with other antimicrobials has been studied by several different investigators and their results have been variously interpreted, depending on strains tested, techniques used, and definitions applied.[6] Some have reported the occurrence of true synergism,[2, 23] but others have not confirmed this.[11, 13] No cross-resistance has been recorded between novobiocin and penicillin, streptomycin, tetracyclines, chloramphenicol, or the erythromycin group of antibiotics.[8]

Absorption, Distribution, and Excretion

Novobiocin is well absorbed from the gastrointestinal tract and maximum plasma levels are reached 1 to 2 hours after an oral dose. Accumulation in the blood is apparent after administration of the first few doses, but this is followed by stabilization with only moderate fluctuations when the drug is given every 6 to 8 hours. Maximal levels appear in the blood earlier and are higher when the antibiotic is administered orally in the fasting state. The ingestion of 0.5 gm. every 6 hours yields plasma concentrations ranging up to 130 micrograms per ml. after a short time; these are many times higher than the in vitro minimal inhibitory levels for susceptible organisms.[21] Considerable activity may be detected in the serum 24 hours after doses of 0.5 to 1.0 gm.

About 3 to 5 per cent of an ingested dose of novobiocin is excreted in the urine; urinary concentrations are several times higher than those in the blood. The major pathway for excretion is biliary and, after a few doses, biliary levels are higher than those in plasma. A large quantity of the antibiotic is present in the feces after oral administration; this represents both unabsorbed drug and biliary excretion.[5, 24]

Novobiocin is distributed throughout body water. It diffuses into pleural, peritoneal, and joint fluids in concentrations lower than those present in plasma. None of the drug is detectable in the spinal fluid of individuals with normal meninges; small quantities may be present in cases of meningitis.[14, 24]

Clinical Use

Novobiocin is an interesting and active antimicrobial, but it is difficult to define for it has a distinctive role among currently available agents. Novobiocin has been used more extensively in the treatment of staphylococcal infections than for infections due to any other bacteria. Most strains of staphylococci are highly susceptible, at least initially. Favorable results have frequently been recorded with the use of novobiocin alone, but most often they were obtained with combinations including other antibiotics, or when novobiocin was added to treatment with other agents to which the offending organisms were at least moderately susceptible. The use of novobiocin, particularly alone, or when given together with other antibiotics to which the staphylococcus is

not susceptible, has been complicated by the development of novobiocin resistance in the staphylococcus during treatment. This has resulted frequently in relapse or extension of the infection after varying degrees of improvement had been achieved.[6] The tendency of staphylococcal lesions to suppurate and encapsulate retards the penetration of the antibiotic to the offending organisms and requires long periods of treatment in order to obtain favorable lasting results. Such prolonged treatment has often been impossible to complete because of sensitization reactions to the drug, which have required its discontinuance. Although novobiocin has been effective in many cases of serious infections, these two factors, the development of resistance in the staphylococcus and of sensitization of the patient to the antibiotic, have limited significantly the full therapeutic potential of this drug in staphylococcal infections. It has often been necessary to resort to other agents to complete the bacteriological and clinical cure.[6, 8, 11] Its once useful place as an antistaphylococcal agent has now been overtaken by the penicillin-resistant penicillins, cephalosporins and other agents which are as active, have bactericidal action and are much less likely to produce untoward reactions which are so common with novobiocin therapy.[8]

Favorable responses have also been observed in infections due to other gram-positive bacteria and in certain cases of urinary tract infections due to gram-negative bacilli, especially those due to Proteus. Moreover, many of the reports have been confused by the use of combinations of novobiocin with other antibacterial agents, chiefly penicillin and tetracycline, so that the true contribution of novobiocin to the results has become even more difficult to define.[6]

Novobiocin has produced favorable results in the treatment of pneumococcal pneumonia and in hemolytic streptococcal infections of the upper respiratory tract, as well as streptococcal cellulitis and scarlet fever. The response of such patients has not been nearly as striking, either bacteriologically or clinically, as that generally observed when penicillin is used in similar cases that are caused by penicillin-sensitive organisms. Failure in cases of pneumonia has been shown to be associated with development of resistant pneumococci.[6]

Staphylococcal enterocolitis, appearing in the course of therapy with other antibiotics, has responded to the oral administration of conventional doses of novobiocin.

Because certain strains of Proteus and of E. coli are susceptible to novobiocin in concentrations that are readily achievable in the urine, this antibiotic has been used in the treatment of a substantial number of cases of urinary tract infections. In vitro resistance increased rapidly in many of these cases, and only a minority of such chronic urinary infections have shown a favorable response that could be attributed to the antibiotic.[6]

Although many strains of H. influenzae and H. pertussis are quite sensitive to novobiocin in vitro, very few cases of clinical infection with these organisms have been treated. Novobiocin has been used successfully to treat brucellosis,[9] but others have not obtained satisfactory results.[6] Wilcox[25] found novobiocin inadequate in the treatment of gonococcal urethritis.

Since staphylococci readily develop resistance to novobiocin, it was suggested early that it could be used in combination with other agents—erythromycin, penicillin, or tetracycline chiefly—and there are many clinical reports of favorable results of such therapy. However, the majority of these reports have dealt with minor surgical infections or with infected dermatoses and only rarely have adequate data been presented from which the respective roles of novobiocin and the other constituents of the mixture could be evaluated. Controlled studies with these combinations have generally not shown any increase in effectiveness and advantage over the use of proper doses of the single agents that they contain.[1, 6, 24]

Indications

Because of the frequency of adverse reactions, many of which are potentially serious, novobiocin should be used only in the rare circumstance of an infection by a susceptible strain of Staphylococcus aureus in a patient hypersensitive to or intolerant of penicillins, cephalosporins, vancomycin, or erythromycin. Novobiocin may also be useful in those rare instances of urinary tract infection by Proteus species shown by in vitro tests to be susceptible to novobiocin but resistant to sulfonamides, penicillin G, gentamicin, or other agents.[15] The combination of novobiocin and tetracycline has been the subject of an adverse report by the Drug Efficacy Committee of the National Academy of Sciences–National Research Council,[18] and the Food and Drug Administration has initiated procedures intended to ban its further distribution.[16] The manufacturer is contesting the ruling in the courts.

Preparations, Routes of Administration, and Dosage

Novobiocin is available in capsules containing 250 mg. of the drug, as a powder (500 mg.) for preparation of solution for injection, and as an oral suspension (125 mg. of novobiocin per 5 ml.). The usual oral dose of novobiocin for adults is 0.5 gm. every 6 hours. Children should receive 20 to 45 mg. per kg. daily, divided into four equal parts and given every 6 hours; for serious disease the daily dose is increased to 100 mg. per kg. The daily intravenous and intramuscular dose is 15 to 30 mg. per kg. in two or three doses, but there is rarely any indication to utilize either of these routes of administration. Novobiocin solutions must be used immediately after preparation; if they become cloudy, they must be discarded.[19, 24]

Untoward Effects

The incidence of reactions to novobiocin is relatively high, ranging from 7 to 20 per cent.[7, 21] The most frequent are hypersensitivity phenomena, chiefly skin eruptions and fever. The rash, which is often extensive and is said to occur in about 12 per cent of treated patients, may be erythematous, urticarial, maculopapular, or scarlatiniform in character. It usually appears between the sixth and twelfth day of treatment.[6, 21] Cutaneous lesions of a hemorrhagic nature may indicate that novobiocin has a coumarin-like effect.[14]

Other reactions following use of novobiocin include serum sickness, Stevens-Johnson syndrome, drug fever, leukopenia, yellowing of the scleras, and, after oral administration, slight abdominal cramping, nausea, and an increased number of stools. Rarely hemolytic anemia, agranulocytosis, thrombocytopenia, and pancytopenia have been reported. About 1 per cent of individuals develop fever, eosinophilia, or leukopenia, alone or together. Rare or uncommon allergic reactions include serum sickness, allergic pneumonitis, and myocarditis. Yellowish discoloration of the plasma, skin, and sclerae may be present in persons receiving novobiocin; this is due to a circulating lipochrome pigment that is a degradation product of the antibiotic. Jaundice with an increase in unconjugated but not conjugated bilirubin in the plasma has been observed in patients receiving conventional doses of novobiocin. Sutherland and Keller[22] found plasma bilirubin levels to be increased three times over normal in newborn infants treated with this drug. They noted a decreased ability of these infants to excrete bilirubin; gross hemolysis or morphological liver damage could not be demonstrated. The cause of this abnormality appears to be inhibition by novobiocin of glucuronyltransferase, the enzyme that catalyzes the conjugation of bilirubin.[21] Because of the possibility of inducing hyperbilirubinemia, administration of novobiocin to newborn and young infants should be avoided. Superinfections caused by novobiocin-resistant bacteria and by fungi have been reported.

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Bacitracin and Tyrothricin

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Bacitracin and tyrothricin are used exclusively as topical or local antibiotics. Because of their toxicity, these compounds have not been used systemically since the development of penicillinase-insensitive penicillins and other safer drugs that are effective against resistant staphylococci.

BACITRACIN

Bacitracin is produced by Bacillus licheniformis, an aerobic, gram-positive, sporulating rod of the Bacillus subtilis group. Three bacitracins, A, B, and C, have been identified. The major constituent of the commercial mix is bacitracin A. Its structural formula has been worked out. The bacitracins are polypeptides containing a thiazolidine ring structure.

Dry bacitracin powder and nonaqueous ointments are very stable at room temperature, but bacitracin quickly deteriorates in aqueous solution and in water-miscible bases if not refrigerated.

The antibiotic activity of bacitracin resembles that of penicillin. Gram-positive cocci are particularly susceptible to bacitracin. It is also active against Corynebacterium, Neisseria, T. pallidum, and Cl. tetani. It does not affect Pseudomonas, Proteus, or Candida.

Bacitracin is bacteriocidal. In the bacterial cell wall it polymerizes to form macromolecules which interfere with proper synthesis of the wall at the time of cell division. It also causes uridine nucleotides to accumulate in the cell.

Bacitracin is used topically in treatment of infections of the skin such as impetigo, infected eczematous dermatitis, infected superficial ulcers, and infected superficial surgical or traumatic wounds. It is also used topically for infections of the external auditory canal, suppurative conjunctivitis, and infected corneal ulcer.

Bacitracin may be used alone for these indications and is very effective when the causative organism is a susceptible one. As bacterial

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cultures and sensitivity studies are infrequently done in these conditions, the activity of bacitracin against gram-positive bacteria is usually supplemented by a compound such as polymyxin B or neomycin, with efficacy against gram-negative organisms, to produce a mixture with a broad spectrum effect. A topical steroid is also included in some of these combinations.

Bacitracin is supplied alone as the U.S.P. ointment. It is also available, combined with one or more of the compounds mentioned above, as an ointment for application to the skin, an ophthalmic ointment, an aerosol spray, and a powder.

Bacitracin applied locally is not irritating, but allergic sensitization has been reported. When a reaction of this type occurs, patch tests should be performed to determine if bacitracin is indeed the culprit, or if another active ingredient or vehicle constituent is the cause. Systemically, the drug is extremely nephrotoxic, but this is not a concern in its topical use.

TYROTHRICIN

Tyrothricin is produced by cultures of Bacillus brevis, a gram-positive, spore-forming, aerobic rod. The antibiotic consists of 80 per cent tyrocidine, a basic cyclic polypeptide, and 20 per cent gramicidin, a neutral polypeptide, of which there are probably four variants. The antibacterial activity is the sum of the activity of the two constituents, but gramicidin is at least two times, and frequently 25 to 100 times, more active than tyrocidine against organisms which are sensitive to both compounds.

Both compounds are active against most gram-positive cocci and bacilli and have only slight activity against a few gram-negative cocci. Their action is attributed to a direct, immediate effect on the permeability barrier provided by the plasma membrane of the cell.

Tyrothricin is no longer used as such, locally or topically, but its more active constituent, gramicidin, is included in a number of combinations for use on the skin, in the eye, and in the ear, nose, and throat. It is effective when susceptible organisms are the cause of the pyoderma, impetigo, infected eczematous dermatitis, infected skin ulcer or wound, or superficial infection of the eye, ear, nose, or throat. It is available in an ointment and cream for use on the skin, in an ophthalmic solution, and in a nasal spray.

Allergic contact dermatitis from the antibiotic occurs rarely. Anosmia and parosmia have been reported from the nasal sprays. Systemic toxicity is marked because of the effect on cellular permeability, so the antibiotic is used only topically.

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Lincomycin: Fact, Fancy, and Future

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Lincomycin is an antibiotic that was first described in 1962. Subsequently, it has been carefully studied in the laboratory and widely used in patients with a variety of bacterial infections. This cumulative experience now permits more precise definition of the relative usefulness of lincomycin in antibacterial chemotherapy. In addition, recognition of certain limitations of the drug has prompted investigation of semisynthetic congeners which may be more active and better tolerated.

DISCOVERY AND CHEMICAL CHARACTERISTICS

Lincomycin is chemically distinct from other available antimicrobial agents. It is elaborated by an actinomycete, Streptomyces lincolnensis, var. lincolnensis, isolated from soil obtained in Lincoln, Nebraska. It was recovered from fermentation broths by Mason, Dietz, and De-boer;[11] it was purified by Herr and Bergy;[25] and its spectrum of antibacterial activity was determined by Lewis, Clapp, and Grady.[37] The molecule is monobasic, composed of a trans-amino acid linked to a sulfur-containing, eight carbon amino-sugar. It is prepared as a hydrochloride salt that is soluble in water, methanol, and ethanol. It is highly stable in crystalline form and in aqueous solutions. Antibacterial activity and stability are not significantly altered by mixture with 5 per cent glucose or saline in physiologic concentrations.

MICROBIOLOGY

Antibacterial Spectrum

The spectrum of microorganisms inhibited by lincomycin is relatively narrow.[31, 37] Among bacteria, it is limited for practical purposes

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to those that are gram-positive. Most group A streptococci, pneumococci, and staphylococci are inhibited by concentrations of lincomycin that are readily achieved in plasma. Clostridia, anthrax bacilli and Corynebacteria are equally susceptible. Some strains of the genus Mycoplasma (M. hominis, M. pneumoniae) are also sensitive; however, most T strains, which may be etiological agents in nongonococcal urethritis, are resistant.[13]

At therapeutically attainable concentrations, lincomycin is inactive against nearly all gram-negative bacteria.[12, 41, 47, 53] In addition, most enterococci (Str. fecalis or Group D streptococci) are resistant. Little or no activity can be demonstrated against tubercle bacilli, most fungi, or true viruses.

Mechanism of Action

Lincomycin inhibits protein biosynthesis in susceptible microorganisms. This activity very likely results from inhibition of binding of amino acid-activated transfer ribonucleic acid to ribosomes.[9, 10, 11, 50] The mechanism of action of lincomycin is very similar to that of erythromycin;[9] and, in fact, antagonism may be observed when bacteria are exposed to the two drugs simultaneously.[22] Antagonism appears more likely to occur when the microorganism is insusceptible to erythromycin.

Lincomycin is primarily a bacteriostatic drug, and should be clearly distinguished in practice from those antimicrobial agents that are almost always bactericidal — penicillins, cephalosporins, polymyxins, and aminoglycosides (streptomycin, neomycin, kanamycin, and gentamicin).[51] Recent advertisements for lincomycin emphasize that "the drug may be either bactericidal or bacteriostatic, depending on the susceptibility of the organism and the concentration of antibiotic."[1] Similar claims could be equally well justified for erythromycin,[1] chloramphenicol,[67] and tetracycline,[6] each of which, in addition to lincomycin, is primarily bacteriostatic against most bacteria at therapeutically attainable concentrations. Minimum bactericidal concentrations of lincomycin usually exceed minimum bacteriostatic levels, often as much as 30-fold.[31]

Development of Drug Resistance

Development of resistance to lincomycin in vitro occurs in a slow, step-wise fashion.[30] Despite this, resistant strains have been encountered among genera that are usually susceptible to lincomycin. De novo resistance has been reported in approximately 15 per cent of strains of Staphylococcus aureus.[12] Insusceptible group A streptococci,[18, 31-55] pneumococci,[17, 54] and viridans streptococci[55] have recently been isolated from patients, many of whom had been previously treated with lincomycin or erythromycin, or both. Also, incomplete cross-resistance among strains of Staphylococcus aureus to lincomycin and erythromycin has been demonstrated in the laboratory and among hospitalized patients.[5, 16] Many of these observations are at variance with current promotional literature from the manufacturers of lincomycin.[50]

CLINICAL PHARMACOLOGY

Oral administration of 500 mg. lincomycin to fasting subjects will produce peak levels (4 hours later) of from 1 to 4 micrograms of drug per ml. of serum.[12, 63] This concentration will inhibit growth of most microorganisms described above as "susceptible."[11-40] However, the presence of food in the stomach may significantly impair absorption of lincomycin, and resultant serum levels may be inadequate to achieve bacteriostasis.[30, 42] Peak serum levels of from 6 to 20 micrograms per ml. are achieved within one hour after intramuscular or intravenous administration of 600 mg.[30, 63] Pain following intramuscular administration of lincomycin is relatively less than that noted with many other antimicrobials. Serum levels obtained after rectal administration of aqueous solutions are approximately one-half of those found when the drug is given orally.[64] Carbowax rectal suppositories containing lincomycin are less well tolerated and produce lower serum levels.[64]

Lincomycin is widely distributed in body fluids and tissues, where concentrations occasionally exceed those found in plasma.[11] The drug crosses the placental barrier and may be detected in amniotic fluid and cord serum. The drug appears in the milk of nursing mothers in concentrations approximating those found in plasma. Penetration into the cerebrospinal fluid is poor or absent in normal subjects. Parenteral administration of 600 mg. of the drug to patients with meningitis results in detectable levels in the spinal fluid;[45] but these levels are not always adequate to inhibit susceptible microorganisms. Penetration of lincomycin into the humors of the eye is poor when the drug is given orally; however, therapeutic levels may be achieved following parenteral administration of 600 mg. of the drug every 4 hours.[1] Perhaps the most advantageous pharmacologic property of lincomycin is its capacity to penetrate bone. Concentrations of active drug in bone are often from one-third to one-half those found simultaneously in plasma.[15, 32]

Orally administered lincomycin is excreted primarily into the bile and feces; only 5 to 25 per cent of the dose appears in the urine.[31, 47, 41] The proportion of the dose excreted by the kidneys increases when the drug is given parenterally. In patients with severe renal disease, blood levels and rates of excretion are three to seven times normal. Peritoneal dialysis or hemodialysis removes little drug from the body.[52]

PREPARATIONS AND DOSAGE

Lincomycin (Lincocin, Upjohn) for oral use is supplied in 250 or 500 mg. capsules, and pediatric drops or syrup containing 250 mg. in each 5 ml. For parenteral therapy, an aqueous solution with 300 mg. of the drug and 9 mg. benzyl alcohol per ml. is available.

Children with mild to moderately severe infections to be treated orally should be given 30 mg. per kg. of body weight daily in three or four divided doses; adults should receive 0.5 to 1.0 gm. three or four times daily, depending upon the severity of the infection. The drug

should be taken no less than 2 hours after or one-half hour before eating. The dosage for parenteral therapy is as follows: (1) children: 10 to 20 mg. per kg. per day in two or three divided doses; (2) adults: 600 mg. two to four times daily. Larger intravenous doses (3 to 20 gm. daily) have occasionally been used in severe or life-threatening infections. No severe reactions were noted with these higher doses; however, phlebitis, superinfections, drowsiness, and paresthesias appeared to occur more frequently.[17, 62] In patients with severe renal disease, the dosage of lincomycin should be lowered to one-quarter to one-third of that noted above. Because of the lack of studies to demonstrate safety, the drug should not be used in newborns, in pregnant women, and in patients with moderately advanced liver disease.

THERAPEUTIC INDICATIONS AND RESULTS OF TREATMENT

In general, lincomycin compares favorably with most antimicrobial drugs in treatment of infections due to susceptible microorganisms. However, it should seldom be the therapeutic agent of first choice; the penicillins and occasionally the cephalosporins are clearly preferable in most diseases due to gram-positive bacteria.[58, 53] Lincomycin may be a useful alternative if the patient is allergic to penicillin or if the infecting microorganism is unresponsive or insusceptible to the penicillins. Lincomycin may be the preferred drug in chronic osteomyelitis due to susceptible microorganisms (see below).

Pharyngitis, otitis, sinusitis, soft-tissue infections, osteomyelitis, pneumonia, endocarditis, and bacteremia due to a variety of susceptible microorganisms have responded well to lincomycin.[19, 21, 23, 27, 39, 46, 60, 66] Mild or moderately severe pneumococcal pneumonia has been shown to respond comparably to lincomycin and penicillin G.[2] Staphylococcal skin infections have responded equally well to lincomycin in comparison with penicillin V and phenethicillin, although adverse reactions were more frequent with lincomycin.[48] In dermatologic practice, carbuncles, furuncles, lymphadenitis, and hidradenitis have been successfully treated.[21, 29] In a double-blind, cross-over study, cystic acne appeared to have been effectively controlled by the drug.

Several studies have demonstrated the efficacy of lincomycin in infections due to the group A streptococci.[7, 8, 28, 51, 57] Patients' clinical and bacteriological responses were often comparable to those noted with penicillin G or phenethicillin given orally. Several recent studies have purported to show superiority of lincomycin over penicillin G in streptococcal pharyngitis,[7, 8, 51] and these are currently being emphasized in promotional literature.[50] However, the failures of penicillin therapy in two of these studies were more common in older children who received only one million units of penicillin G daily.[7, 51] In addition, diarrhea and posttreatment elevation of erythrocyte sedimentation rates were more frequent in patients receiving lincomycin. The efficacy of lincomycin in prevention of rheumatic fever has not been established.

Lincomycin appears to be uniquely effective in chronic osteomyelitis, especially that due to susceptible coagulase-positive staphylococci.[21, 26, 27, 31] Many patients who have previously failed to respond to prolonged courses of the penicillins and other antimicrobials have shown dramatic improvement with lincomycin. The drug has been most beneficial when given for several months in a dose of 2 gm. or more daily. Its efficacy in chronic osteomyelitis correlates well with the relatively high levels of active drug found in bone.[15, 32] Lincomycin appears to offer little or no significant advantage over other antimicrobial agents in management of acute osteomyelitis.

Since resistant strains have been encountered among most gram-positive bacteria (pneumococci, staphylococci, Group A streptococci, and viridans streptococci), susceptibility to lincomycin should always be established by appropriate culture and laboratory studies. Although infrequent, resistant mutants may emerge during therapy. Because of possible mutual antagonism and similar spectra of action, erythromycin and lincomycin should never be administered simultaneously.

ADVERSE REACTIONS TO THERAPY

Gastrointestinal irritation is the most frequent adverse reaction to lincomycin. Diarrhea of varying severity may be encountered in from 5 to 50 per cent of patients.[31, 49, 53] It is more likely to occur with oral administration of the drug, but may be noted with parenteral therapy as well. Occasionally, the reaction may progress to include many or all of the following: fever, severe abdominal cramps, tenesmus, intestinal distention, leukocytosis, and blood, mucus, and pus in the stool.[31] Sigmoidoscopic examination will then usually reveal hyperemic, edematous, and friable mucosa without ulceration. These signs and symptoms, once present, may persist for several weeks following discontinuation of the drug. The author has seen two patients who were subjected to exploratory laparotomy for abdominal colic with distention, fever, and leukocytosis—which most likely resulted from administration of lincomycin. Unfortunately, it is impossible to predict which patients will progress to more severe gastrointestinal symptoms among those who develop only diarrhea initially. Therefore, when diarrhea occurs in patients receiving lincomycin, it may be advisable to substitute an alternative drug whenever possible.

Despite its relatively narrow spectrum of antimicrobial activity, lincomycin may be associated with superinfection with resistant microorganisms, particularly Candida albicans. Superinfections are more likely to occur with prolonged treatment or when higher doses are used. The drug appears to be especially prone to aggravation of pre-existing Candida vaginitis or thrush, occasionally after only a few doses. Lincomycin should be used with caution in these patients. Individuals who are highly vulnerable to superinfection (patients with poorly controlled diabetes, immune-deficiency diseases or disseminated malignancies) should be examined carefully at frequent intervals.

Other adverse effects of lincomycin are relatively uncommon. Occasional hypersensitivity reactions, such as a variety of skin rashes, drug fever, angioneurotic edema, urticaria, serum sickness, and anaphylaxis, have been observed. Transient depression of hematopoiesis, jaundice, and abnormal liver function tests without symptoms also have been noted infrequently.

CONGENERS OF LINCOMYCIN

A variety of chemical modifications of the lincomycin molecule have been produced in an attempt to improve upon the parent drug.[10] Among the most promising are those in which a chlorine atom has been substituted for the hydroxyl group in the 7-position of lincomycin (clinimycin, clindamycin, Dalacin-C). The chlorinated derivatives share the antibacterial spectrum of the parent compound, but appear to be more active against susceptible bacteria in vitro.[20, 43, 45, 48] Absorption and excretion occur more rapidly.[43, 65] Gastrointestinal absorption is delayed but not diminished by the presence of food in the stomach.[65] Half-life in serum may be prolonged in patients with renal disease, with or without hemodialysis.[11] Favorable responses to therapy have been noted in limited numbers of patients with pneumonia, bronchitis, soft-tissue infection, streptococcal pharyngitis, and osteomyelitis.[5, 48, 56] Clinical investigators have thus far concluded that the chlorinated derivatives are effective, but not superior to related drugs in therapy. Unfortunately, in limited studies to date, diarrhea appears to have occurred with equal frequency in patients treated with lincomycin and its congeners. Interestingly, the 7-halogenated derivatives appear to possess activity against malaria in experimental animals.[36]

SUMMARY

Lincomycin inhibits growth of many gram-positive pyogenic bacteria in vitro and in vivo. Its action is primarily bacteriostatic. The drug is moderately well absorbed from the gastrointestinal tract only in the fasting state. Results of treatment of many infections due to susceptible microorganisms have compared favorably with those achieved with other available antimicrobial agents. The drug has produced superior results in patients with chronic staphylococcal osteomyelitis. A syndrome resembling ulcerative colitis may supervene in patients who experience diarrhea while on lincomycin. The frequent occurrence of diarrhea and the unpredictable nature of the more severe gastrointestinal sequelae are factors limiting its usefulness.

Lincomycin may be useful as an alternative to the penicillins. However, erythromycin, which is similar in antibacterial spectrum and pharmacologic characteristics, may be preferable because of its greater potency and less frequent side effects.[53] Use of lincomycin should always be accompanied by appropriate cultures and tests of

bacterial susceptibility. It should seldom be used in newborns, in pregnant women, or in patients with advanced liver disease. It should never be administered simultaneously with erythromycin.

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Gentamicin

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Although the isolation of gentamicin[†] was first reported in 1963,[29] it was not until April 1969 that this antibiotic became available for commercial use in the United States. This 6 year hiatus between discovery and general use of the drug provided the opportunity for investigators to evaluate the potential value as well as the limitations of gentamicin, and resulted in the somewhat unique situation of a new antibiotic released for distribution with a clearly defined place in the antimicrobial armamentarium.

Initial studies in 1963[16, 17, 26, 29] demonstrated that the antibacterial spectrum of gentamicin was broader than that of any other available antimicrobial agent. Other studies[1] demonstrated that the physical and pharmacologic properties of gentamicin were satisfactory and that it was clinically effective for serious gram-negative infections caused by any one of the Enterobacteriaceae as well as pseudomonas species.[16, 17] These observations seemed timely and seemingly portended the availability of a needed antibiotic coincident with the rising incidence of serious gram-negative infections.

It was soon noted, however,[16, 17] that gentamicin possessed ototoxic properties similar to the ototoxic properties of the antibiotics structurally related to gentamicin – kanamycin, neomycin, and streptomycin. Although these initial observations of ototoxicity were sporadic and were quite quickly shown to have been related to excessive dosage in patients with impaired renal function, the general use of gentamicin was wisely delayed pending more extensive evaluation.[14] During the ensuing 5 or 6 years an extensive number of laboratory and clinical studies of gentamicin were reported, and two major interdisciplinary symposia[10, 15] were held to provide a means for dissemination of information on gentamicin. Our studies with gentamicin began in 1963 and, although primarily confined to the treatment of urinary tract infectious disease, have necessarily been related to the clinical assessment of gentamicin as portrayed in this communication.[3-5]

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PRODUCTION, STRUCTURE, AND PHYSICAL PROPERTIES

Gentamicin[30] is produced from the submerged fermentation products of several microorganisms in the genus Micromonospora and the family Actinomycetales. Prior to the isolation of gentamicin, the Micromonospora had not been screened for antibiotic production and to date gentamicin remains the only clinically available antibiotic which is produced by this genus. On the other hand, the genus Streptomyces, in the same family of microorganisms, has produced a variety of antibacterials, such as streptomycin, the various tetracyclines, chloramphenicol, neomycin, kanamycin, and lincomycin.

The chemical structure of gentamicin[30] is similar to that of streptomycin, kanamycin, and neomycin in that all four antibiotics contain two amino-sugar molecules in their structure; hence, the classification of these antimicrobials as "the aminoglycoside antibiotics." In addition to the two amino-sugars, the structure of gentamicin, kanamycin, and neomycin is completed by a third amino-sugar, deoxystreptomine. Therefore, these three antibiotics are often referred to as "the deoxystreptomine antibiotics." It has also been shown[2] that gentamicin is a complex of three antibiotics (designated gentamicins C1, C2 and C1a) which differ in structure only by one or two CH_3 groups. Most importantly, the antibacterial activity and toxicity of these individual components of the complex are virtually the same and do not differ from the complex produced for commercial use.

Gentamicin is a basic compound which is water soluble and colorless, and is available as the sulfate salt as an odorless powder which in aqueous solution does not require refrigeration. The drug is uniquely stable to extremes of temperature and pH range.

ANTIMICROBIAL SPECTRUM

The most unusual feature of gentamicin is, without question, its unusually wide spectrum of activity against gram-negative and gram-positive bacteria. The initial observation that gentamicin was active against pseudomonas as well as proteus species was clearly unique, and this dual antibacterial activity is still probably the single most important attribute of gentamicin.

In general, gentamicin is effective against all Enterobacteriaceae, pseudomonas species, and penicillinase and non-penicillinase producing staphylococci. Data from our laboratory compiled in 1968 (Table 1) and those data reported by other investigators[9, 13, 16-18, 26, 29] strongly support this spectrum of activity. It is equally clear from these data that the enterococcus (Streptococcus fecalis) is not sensitive to gentamicin. In addition to the organisms listed above, gentamicin appears to be effective for a variety of other pathogens.[9, 28] However, because the data is too meager in some instances, and in others gentamicin would not be a suitable antibiotic choice even if effective, these bacterial species will not be discussed here. However, it is probably noteworthy to point out that gentamicin is not highly active against meningococci.[28]

Table 1. *Gentamicin: Disc-sensitivity Results, 2900 Consecutive Urinary Pathogens: Isolated During 1967 and 1968*[*]

| ORGANISM | NO. ISOLATES TESTED | SENSITIVE TO GENTAMICIN DISC | |
		2 micrograms	10 micrograms
E. Coli	600	569 (95.0%)	594 (99.0%)
Klebsiella-aerobacter	300	281 (93.3%)	290 (96.6%)
P. mirabilis	300	251 (83.6%)	274 (91.3%)
indole-positive proteus	200	174 (87.0%)	186 (93.0%)
other coliforms	150	141 (94.0%)	147 (98.0%)
pseudomonas	500	443 (88.6%)	486 (97.2%)
B. anitratum	40	34 (85.0%)	39 (98.0%)

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It has been shown that a standardized disc-diffusion technique for gentamicin, using a commercially available 10 microgram disc, is satisfactory for the differentiation of sensitive and resistant organisms in most clinical situations. The vast majority of organisms shown to be sensitive to gentamicin by this technique will be inhibited by 5 to 6 micrograms per ml. or less of the drug. In other words, the determination of the minimal inhibitory concentration (MIC) of the infecting bacterium is not necessary in most clinical situations. A possible exception to this generalization is noted in a recent report by Traub[27] (and to a lesser extent in our own laboratory) that pseudomonas species are prone to produce erratic and often small zones of inhibition about a 10 microgram gentamicin disc. For this reason, questionable pseudomonas zones (10 to 12 mm.) should probably be confirmed by MIC studies, since, contrary to the implication of the small zone size, the strains may, in fact, be quite sensitive (i.e., have a low MIC).

It is most appropriate, in light of the increased incidence of hospital-acquired gram-negative infections, to emphasize the in vitro anti-microbial spectrum of gentamicin as it applies to Enterobacteriaceae and pseudomonas, because it is here that gentamicin finds its greatest clinical value. It has been repeatedly shown that, when evaluated by disc sensitivity studies, 90 per cent or more of the following organisms are sensitive to gentamicin: E. coli, klebsiella, enterobacter species, Proteus mirabilis, indole positive proteus species, "other coliforms," Serratia marcescens, and pseudomonas species. Other reports[9] have shown that when these organisms are sensitive, the MIC is most often 5 to 6 micrograms per ml. or less (Table 2). The few strains not inhibited by this level of the drug are usually susceptible to the next antibiotic dilution (i.e., 10 to 12 micrograms per ml.). This difference can be important, since a serum level of 5 to 6 micrograms per ml. can be easily attained and is well tolerated, whereas, although serum levels of 10 to 12 micrograms per ml. can be reached, this level is potentially toxic and the margin of safety becomes less secure. Proteus species (both indole-positive and indole-negative), although clearly sensitive to gentamicin, appear to require slightly more drug for inhibition than do the other Enterobacteriaceae. Furthermore, although the data is

Table 2. *Gentamicin Minimum Inhibitory Concentrations, 600 Consecutive Urinary Pathogens**

ORGANISMS	NO. ISOLATES TESTED	MINIMUM INHIBITORY CONCENTRATION (micrograms per ml.)									PER CENT SENSITIVE TO 6.25 MICROGRAMS PER ML. OR LESS
		0.39 or <	0.78	1.56	3.12	6.25	12.5	25	50	100 or >	
Pseudomonas	150	14	22	51	40	19	2	1		1	97%
E. coli	100		6	10	40	33	10		1		89%
Klebsiella-aerobacter	100	9	20	48	17	3	2			1	97%
Intermediate coliforms	50	6	9	19	11	3	1			1	96%
Proteus mirabilis	100			12	22	34	28	3	1		68%
Indole-positive proteus	50	6	8	8	10		10	1	1		76%
Staphylococcus	25			2	8		1				96%
Enterococcus	25							3	10	12	0
Total strains examined	600										

limited, certain organisms of the klebsiella-aerobacter group (i.e., Enterobacter cloacae) appear to be less sensitive than the remainder (and majority) of the group. Also of note is the high degree of sensitivity of serratia to gentamicin, an important observation in light of the increasing incidence of hospital-acquired serratia infections. Although the clinical need is not apparent at present, it is interesting to point out that a large volume of in vitro data has shown that staphylococci are very sensitive to gentamicin.[12]

RESISTANCE, SYNERGISM AND MECHANISM OF ACTIVITY

As with other antimicrobial agents, chromosomal resistance to gentamicin can be induced in vitro by repeated subcultures in less than inhibitory concentrations of the antibiotic. Unlike the facultative or "single-step" mutation resistance which can be induced to strepto-mycin, induced resistance to the other aminoglycosides is a "multiple-step" phenomenon.[3] Induced resistance of this type is accompanied by cross-resistance to kanamycin and neomycin; similarly, induced resistance to kanamycin or neomycin is associated with gentamicin cross-resistance. On the other hand, when kanamycin resistant bacteria are obtained from patients, they have been (in our experience and that of others[9]) sensitive to gentamicin. Development of resistance to gentamicin in clinical practice does not occur often and, when seen, it is usually associated with gentamicin therapy in patients with indwelling urinary catheters or similar communications to the exterior. Spontaneous development (without prior drug exposure) of significant resistance to gentamicin, due either to mutation of the bacterial chromosome or to extrachromosomal R factors, to date appears to be a very rare occurrence.

Like the other aminoglycosides, gentamicin is a bactericidal antibiotic. Bactericidal concentrations are usually the same as or two times the inhibitory concentration. Antibacterial activity is accomplished by inhibition of bacterial protein synthesis (RNA misreading[11]). The most notable environmental effect (in vitro) upon the antibacterial activity of gentamicin is the pH of the medium. The antibiotic is much more effective in an alkaline medium, an observation of theoretical importance in urinary infections. However, to date, there have been no controlled clinical trials in this regard. Increasing concentrations of sodium chloride also exert an inhibitory effect on the activity of gentamicin. Serum binding of 25 to 35 per cent results in a proportionate decrease in activity—an observation of doubtful clinical significance.

Until recently, evidence of synergistic effects when gentamicin was combined with other antibiotics has been limited. A few in vitro studies, and even fewer clinical studies, have suggested that gentamicin in combination with tetracycline, ampicillin, or the polymyxins may exert a synergistic effect. However, the effects vary considerably for each antibiotic pair and depend upon the bacterial species under study.

On the other hand, several recent reports[2, 1] have rather consistently demonstrated in vitro synergism as well as a synergistic effect during treatment of pseudomonas species with a combination of gentamicin and carbenicillin. Considering the tenaciousness of some pseudomonas infections, further investigation of this antibiotic combination seems warranted. However, the use of possible synergistic combinations is probably necessary only in those occasional patients in whom potentially toxic levels of gentamicin are required to inhibit the infecting organism.

PHARMACOLOGY, DOSAGE, AND TOXICOLOGY

Gentamicin is currently available for oral, topical, and parenteral (intramuscular) injection. Orally the drug is very poorly absorbed (up to 2 per cent recovery in the urine) except during the acute stage of bacillary dysentery when as much as 10 per cent of an administered dose may be recovered from the urine.[3] Gentamicin should never be administered orally for systemic therapy. When applied topically to the skin in a 0.1 per cent ointment or a 0.1 per cent cream, up to 2 per cent of the drug may be recovered from the urine within 72 hours. It should be stressed, however, that when applied to large areas of denuded epithelium, such as in burn patients, significant (although usually subinhibitory) systemic absorption usually occurs. Serum levels of up to 1.0 microgram per ml. and renal excretion of 2 to 5 per cent have been reported following topical application in these patients.

Gentamicin[1] is rapidly and completely absorbed from the site of intramuscular injection with resultant peak serum levels occurring within 30 to 60 minutes. The serum half-life is $2\frac{1}{2}$ to 4 hours, but demonstrable gentamicin activity is usually present at 8 to 10 hours after injection of recommended doses. A usual individual dose of gentamicin (0.8 to 1.0 mg. per kg. body weight) produces serum levels ranging from 4 to 10 micrograms per ml. and averaging about 7 micrograms per ml., and trough levels are 0.5 to 2.0 micrograms per ml. In patients with normal or near normal renal function, repeated doses at intervals does not lead to significant accumulation of gentamicin in the serum. On the other hand, with impaired renal function, the serum half-life is prolonged, and if the dosage is not reduced (or the intervals between doses are not increased) potentially toxic levels of gentamicin will accumulate.

There is very little alteration or detoxification of gentamicin by the host, and virtually all of the administered drug (in repeated doses) is eliminated in its active form by the kidney. This is accomplished by glomerular filtration, and the clearance of gentamicin roughly parallels that of creatinine. Gentamicin is distributed throughout the extracellular space and only small amounts are excreted in the bile. Urinary gentamicin concentrations (levels) are dependent upon the glomerular filtration rate and vary considerably with changes in urinary volume. Urinary levels of gentamicin have been shown by us and others[1, 16, 17] to range from 5 to 100 micrograms per ml. and, except

in cases of very severe renal impairment, are usually at least three times the peak serum level.[9]

Cerebrospinal fluid levels of gentamicin (following systemic administration) are quite low in patients with normal meninges. We have measured gentamicin concentration in the cerebrospinal fluid of 18 patients without meningitis 1 to 10 hours following a single 80 mg. intramuscular dose and have found the levels to range from 0 to 0.4 microgram per ml.[6] Cerebrospinal fluid levels have been measured sporadically in patients with inflamed meninges, and although these levels are higher than those in patients with normal meninges, they are often subinhibitory. Therefore, supplemental intrathecal or intraventricular administration seems indicated when gram-negative meningitis is to be treated with systemic gentamicin. In inflamed serous cavities, gentamicin levels are about one-half the serum level.[9] Gentamicin can be effectively removed from anuric patients by hemodialysis as well as peritoneal dialysis.

The package insert for gentamicin currently recommends a dosage range of from 0.8 to 5.0 mg. per kg. per day, administered in two to four equally divided doses, with appropriate reduction in dosage for patients with impaired renal function. Although this dosage recommendation is satisfactory with respect to the maximum dose, a minimum dose of less than 2.5 mg. per kg. per day is rarely justified in patients with normal renal function. From a practical standpoint, doses of 60 to 80 mg. three to four times daily (i.e., 180 to 320 mg. per day) are convenient and satisfactory for most clinical situations. Obviously, heavier patients with very severe infections require calculation of the full 5 mg. per kg. per day dose. As mentioned above, for patients with reduced renal function, the dosage of gentamicin must be reduced. Rather than reducing the mg. dosage of each individual dose, we currently recommend that 60 to 80 mg. be administered initially and that subsequent doses be given at more prolonged intervals. For patients with impaired renal function the following is recommended: (1) BUN of 25 to 40 mg. per 100 ml., 60 to 80 mg. twice daily; (2) BUN of 40 to 70 mg. per 100 ml., 60 to 80 mg. once daily; (3) BUN of 70 to 100 mg. per 100 ml., 60 to 80 mg. every other day; (4) BUN of greater than 100 mg. per 100 ml., 60 to 80 mg. every third day; and, (5) patients on twice weekly hemodialysis, 60 to 80 mg. after each dialysis. If facilities for bioassay are available, dosage is adjusted to prevent accumulation of serum levels in excess of 10 to 12 micrograms per ml.

Neither side effects nor toxicity has been reported following the oral administration of gentamicin.[9] Topical application of gentamicin cream or ointment is well tolerated and is apparently relatively free of local irritation and sensitization except possibly in patients with eczema who are sensitive to the other deoxystreptomine antibiotics.[9]

Parenteral administration by intramuscular injection is well tolerated and does not produce local sensitization. Allergic skin rashes are rare; we have seen only one such occurrence in six years. The drug has not been associated with hepatic or hematopoietic toxicity.

Renal toxicity in association with therapeutic doses of gentamicin is infrequent, with an estimated incidence of 2 per cent or less.[7] Renal

toxicity, a potential hazard with all aminoglycoside antibiotics (especially neomycin), is usually manifested by nitrogen retention as evidenced by a rising BUN. Most often this occurs in patients with pre-existent renal damage (often without adequate dosage reduction) and fortunately it is usually reversible. The renal lesions which can be produced in animals with very large (well above the human therapeutic range) doses of gentamicin apparently are not applicable to human therapy within the therapeutic ranges utilized to date.

Ototoxicity is the only consistent and clearly the most serious toxic effect which can result from gentamicin therapy. Unlike kanamycin, which primarily affects the auditory portion of the eighth cranial nerve, gentamicin toxicity primarily involves the vestibular apparatus. The first clinical evidence of such toxicity from gentamicin was reported in 1964.[16, 17] In that study, five of 53 patients receiving gentamicin developed labyrinthine damage, which was bilateral and permanent in three of these. It was noted that four of the five patients were azotemic and the fifth received a large total dose. Vestibular damage appeared after at least one week of therapy, and in some patients, several days after therapy. As a few similar cases were reported by other investigators at about the same time extensive clinical trials were curtailed pending clarification of the underlying factors predisposing to gentamicin vestibular toxicity. It was soon shown that gentamicin ototoxicity occurred primarily (and possibly exclusively) in those patients with impaired renal function who received high doses and attained serum levels in excess of 10 micrograms per ml.[3] Also, many of the affected patients had previously received ototoxic drugs or had pre-existing otologic disease. Later, more carefully monitored clinical trials demonstrated that the incidence of gentamicin-induced permanent vestibular damage could be greatly lowered by application of the above principles. Furthermore, if gentamicin therapy were discontinued at the earliest indication of vestibular impairment, the process was most often completely reversible. It is currently estimated that 2 to 2.5 per cent of patients treated with parenteral gentamicin exhibit some evidence of vestibular toxicity,[3] either bilateral or unilateral. However, the incidence of permanent vestibular dysfunction is probably of less magnitude. Auditory loss, except for occasional loss of high frequency perception, has been rare.

CLINICAL APPLICATION

The following is not an attempt to discuss in detail the entire clinical experience with gentamicin but rather is an attempt to briefly discuss the various types of infections for which gentamicin has most commonly been utilized. In general, by application of the known bacteriologic data and clinical pharmacology, the outcome of gentamicin therapy for individual infectious disease problems should be reasonably predictable in advance.

Gram-negative bacteremia.   Some of the most dramatic responses to gentamicin therapy have been noted in patients with gram-negative

sepsis. Two reports[23, 31] record a total of 20 of 46 patients with bacteremia surviving with gentamicin therapy. Other investigators[22] have reported that gentamicin is effective for gram-negative sepsis in the pediatric age groups. In the only controlled study published to date, Martin et al.[21] demonstrated that gentamicin (with or without cephaloridine in combination) was the most effective therapy for patients with gram-negative bacteremia. The other antibiotic regimens tested were: kanamycin plus polymyxin B or colistimethate, and cephaloridine plus either polymyxin B or colistimethate (a total of six treatment groups). Since the use of six treatment groups necessarily reduced the number of patients in each group, we subsequently instituted, and recently reported,[5] a study in which patients with gram-negative bacteremia were randomly placed in one of two antibiotic treatment groups, (1) those receiving gentamicin only (41 patients), or (2) those receiving a combination of polymyxin B and kanamycin (34 patients). There was an 85.4 per cent survival rate in the gentamicin group and an 82.3 per cent survival rate in the polymyxin B-kanamycin group. Other criteria of therapeutic response (temperature response, reversal of hypotension, and eradication of primary infection) were as good or superior in the gentamicin group. It was concluded that gentamicin is satisfactory and is probably the antibiotic of choice for gram-negative bacteremia. This is especially true prior to identification of the exact gram-negative species involved.

URINARY TRACT INFECTIONS. The antibacterial spectrum and pharmacology of gentamicin are ideally suited for the therapy of urinary tract infections. With the exception of enterococcal infections, all microbial contingencies are "covered." Apparently this potential efficacy for urinary infection did not go unnoticed, as by far the greatest experience with the parenteral use of gentamicin has been for this infection. Of the multitude of reports available, the following observations were most consistently noted: (1) 90 to 95 per cent of the organisms (except enterococci) recovered from patients with urinary tract infection were susceptible to gentamicin; (2) susceptible bacteria were inhibited by concentrations of gentamicin easily attainable in the serum and far below urinary concentrations; (3) gentamicin is as effective or more-so than the polymyxins (polymyxin B or colistimethate) for pseudomonas, E. coli, and klebsiella-enterobacter infections; (4) gentamicin is more effective than kanamycin for infections caused by all proteus species as well as for those caused by E. coli and klebsiella-enterobacter; (5) gentamicin is effective, but no more so that many other antibiotics, for simple uncomplicated urinary infections; and (6) gentamicin, in selected cases, may be more effective than other agents in curing recurrent or persistent (often complicated) urinary infection.

The most difficult problem is deciding when to use gentamicin for urinary tract infectious disease. It is probably prudent to recommend that the drug be reserved for those infections resistant to or failing to respond clinically to the common less effective antimicrobial agents.

PULMONARY GRAM-NEGATIVE INFECTIONS. The reported experience with gentamicin therapy for gram-negative pulmonary infection is not extensive and was recently reviewed by Louria et al.[19] Forty-five of

the 75 recorded cases were pseudomonas infections, with klebsiella-aerobacter a distant second. Most patients were treated as a "last resort" after failing to respond to other antibacterials. Forty per cent of the patients without underlying pulmonary disease and 20 per cent with underlying disease responded to gentamicin therapy. Although these percentages are low, it should be pointed out that other agents had failed. In addition, superinfections were remarkably few.

Infections associated with burns. Four different groups have each reported excellent results with the topical and parenteral use of gentamicin for burn patients.[9] Very satisfactory results have been noted in the treatment of pseudomonas sepsis associated with burns. One investigator[25] reported a reduction in mortality from 100 per cent to 20 per cent in patients treated with gentamicin for burns associated with pseudomonas sepsis and verdiglobinuria. Another group,[20] in a comparative study, reported that gentamicin, used topically and systemically, resulted in lower mortality and more rapid healing than did the other therapy groups.

Other infections. Thirty-six cases of meningitis (33 due to gram-negative organisms) treated with gentamicin have been reported.[9] Apparently, in all cases intramuscular administration was supplemented by intraventricular or intrathecal injections. A successful outcome was recorded in all but seven of these cases. A wide variety of other infections[9] have been treated with gentamicin, but results are difficult to interpret owing to the small numbers of patients reported. Varying numbers of cases of peritonitis, salpingitis, prostatitis, infected wounds, cellulitis, biliary tract infections, and osteomyelitis are among those reported. Results in these infections were generally described as good.

One group[8] treated 140 patients with ear, nose, and throat diseases, 119 for infection and 21 for prophylaxis. Thirty-two additional such patients were treated by three other groups. Results were reported as good, and only 5 per cent of the cases were considered as treatment failures.

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Ethambutol and Viomycin

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ETHAMBUTOL

When a new chemotherapeutic agent is introduced into the medical literature, it is a matter of conscience "to tell it like it is." This we shall try to do in respect to ethambutol (Myambutol), a new orally administered agent for the treatment of mycobacterial infections.

Bacteriology, Chemistry, and Pharmacology

A synthetic compound developed by Lederle Laboratories, ethambutol has a specific antimicrobial effect against organisms of the genus Mycobacterium, being essentially inactive against other bacteria, fungi, and viruses.[6] The new drug is characterized by unique structural and stereochemical specificity. The generic name "ethambutol" is restricted to the dextrorotatory isomer of the compound 2,2 (ethylenediiminodi-1-butanol hydrochloride), the therapeutically active substance.[22]

From a chemical standpoint ethambutol is different from all other antimycobacterial agents. There is no cross-bacterial resistance between this drug and any other agent, and it is compatible with all other agents in use today. Studies using electron microscopy suggest that ethambutol exerts its antimicrobial effect by inhibiting the synthesis of ribonucleic acid.[3]

Mycobacterium tuberculosis and M. bovis are highly susceptible to ethambutol in vitro. In our laboratory, ethambutol is incorporated in Herrold's glycerinated egg yolk agar in concentrations of 2, 5, and 10 micrograms per ml. Before exposure to the drug, nearly all strains of M. tuberculosis are completely inhibited by the lowest concentration. Most strains of M. kansasii are also highly susceptible to ethambutol, but the susceptibility of mycobacteria in Runyon's groups II, III, and IV tends to be limited or nil. Some nonchromogens and a few scotochromogens exhibit appreciable susceptibility to ethambutol in vitro, but all of the rapid growers, including M. fortuitum, are highly resistant to the drug.

Ethambutol proved to have a marked suppressive effect in experimental tuberculosis of mice, guinea pigs, and monkeys.[7, 19, 22] Toxic

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effects occurred only when the drug was administered in doses many times as large as the dosage recommended for human beings.

The pharmacology of ethambutol has been studied extensively. It is absorbed rapidly from the gastrointestinal tract and is excreted mainly by the kidneys. There is little, if any, accumulation in the tissues. The drug is not extensively metabolized, approximately 10 per cent being converted to therapeutically inactive metabolites.[12]

Ethambutol is administered orally in one dose per day. Absorption and serum concentrations are not reduced by the ingestion of food. Serum concentrations are proportional to dosage and are usually maximal from 2 to 4 hours after the ingestion of a single oral dose. With a dose of 15 to 25 mg. per kg. of body weight, serum levels of 2 to 5 micrograms per ml. are produced. Ethambutol does not pass through intact meninges but does appear in therapeutic concentrations in the cerebrospinal fluid of patients with tuberculous meningitis.[13]

Clinical Application and Dosage

The clinical usefulness of ethambutol has been proved by many investigators. Ethambutol is not a substitute for INH (isoniazid), the best antituberculosis agent available to date, but the new drug is generally considered to be superior to para-aminosalicylic acid (PAS) as an adjunct to INH in initial treatment.

Ethambutol is prescribed on the basis of body weight. Serum concentration cannot be used as the basis for dosage because of the lack of a practical method of determination.

This is not a drug which can be given in a routine dose. Ethambutol should be prescribed in a dose of 15 to 25 mg. per kg. of body weight, and in each case the dose should be calculated with care, the total daily amount being rounded off to the nearest 100 mg. (The drug is available in tablets of 100 mg. and 400 mg.) As long as the patient is under treatment, he should be weighed at least once a month and the dose of ethambutol adjusted for changes in weight.

In one regimen used frequently, ethambutol is given in a dose of 25 mg. per kg. of body weight for 2 months; thereafter, in a dose of 15 mg. per kg. In another regimen, it is given in a dose of 15 mg. per kg. throughout treatment.

At the Chicago State Tuberculosis Sanitarium our standard dose of ethambutol is 20 mg. per kg. of body weight throughout treatment. In our 9 years of experience, we have found the drug both safe and effective when used in this dosage. In an early clinical study in which ethambutol was administered alone to patients having extensive drug-resistant tuberculosis, bacteriologic improvement occurred consistently with a dose of 20 mg. per kg. but rarely with a dose of 15 to 17 mg. per kg. In retreatment cases in which ethambutol is combined with other agents having low therapeutic indices, it is especially important to administer ethambutol (as well as the other agents) in doses which are truly therapeutic.

Among patients with normal renal function there is no objection to giving ethambutol in a dose of 25 mg. per kg. during the first 2 months

of treatment and, in fact, an initial high dose is advisable in some cases of tuberculosis meningitis or other critical situations.

In prescribing ethambutol, some attention should be given to the patient's renal function. When the urea nitrogen is significantly elevated or when other studies indicate poor renal function, the dose of ethambutol should be reduced proportionately.

Toxicity

Ethambutol has now been administered to thousands of persons. The only significant form of toxicity has been the occurrence of ocular toxicity which is dose-related and reversible. In the doses recommended currently, ocular toxicity is uncommon and the potential risk is small.

In early clinical studies when ethambutol was given in a dose of approximately 50 mg. per kg. of body weight per day, ocular toxicity occurred in a sizable proportion of cases.[8, 12, 15] Signs and symptoms were consistent with retrobulbar neuritis, including decreased visual acuity, loss of color discrimination, constriction of the visual fields, and central and peripheral scotomata. There were no funduscopic changes and no increase in ocular tension.

Even in the most severe cases, ocular toxicity proved to be reversible over a period of weeks to months. In our own experience it has been reversible in all cases, and this has also been the experience of most other investigators. Documented cases of permanent visual defects caused by ethambutol are rare.

When the average daily dose was decreased to 25 mg. per kg. of body weight, the incidence of visual toxicity was greatly reduced. When the dose was decreased to 20 mg. per kg. or less, the danger of ocular toxicity became negligible. In our total series of 600 patients treated with ethambutol in a dose of 20 to 25 mg. per kg. for a minimum of 3 months, there have been 6 cases of definite or possible ocular toxicity, an incidence of 1 per cent. All six patients had received ethambutol in a dose of 23 to 25 mg. per kg. for periods of 4 to 13 months.

In the package circular distributed with Myambutol (ethambutol), it is stated that "approximately 6 per cent of patients who have received Myambutol have exhibited decreases in visual acuity." This statement is misleading. In all reports on the use of ethambutol in the doses currently recommended, the incidence of definite ocular toxicity is very low. In a total of 174 patients, Bobrowitz and Robins[2] noted one case. In cooperative studies conducted by the United States Public Health Service, more than 1100 patients received ethambutol in doses of 15 mg. or 6 mg. per kg. of body weight. Decrease in vision was no more frequent with the larger dose than with the smaller dose, and the proportion of patients with a significant decrease in the groups of patients receiving ethambutol was no greater than in another large group receiving drugs which did not include ethambutol.[10]

It has been learned that in successive tests a patient's visual acuity may vary by one or two lines of the Snellen chart before treatment with ethambutol is begun. Therefore it is recommended that the visual acuity of each patient be tested initially at least twice. Moreover, a

decrease of only one or two lines during treatment with ethambutol is not significant unless the patient complains of blurred vision or unless there are other indications of ocular toxicity.

It is important to establish a good base line, and therefore the patient's initial examination should include funduscopy, determination of visual fields, and assessment of his ability to see red and green colors. Leibold has stated that in ethambutol toxicity, blurred vision, and loss of ability to see green color have always occurred together.[8]

It is usually recommended that patients have monthly examinations of their visual acuity during treatment with ethambutol, the eyes being tested separately and together, with glasses if these are worn by the patient. There is some doubt that this is necessary. In most cases of ethambutol toxicity the patient is aware of his difficulty as soon as the visual acuity decreases. In fact, subjective findings may precede the objective evidence of toxicity. If patients are instructed to report any visual changes promptly, routine testing of the visual acuity probably is unnecessary. Of course patients who are unable to carry out instructions, those with poor renal function, and those who had ocular abnormalities initially must be watched closely. In the presence of visual defects such as cataracts and diabetic retinopathy, the need for treatment with ethambutol must be weighed against the difficulty of detecting and evaluating changes in vision.

When a significant decrease in vision or any other abnormality occurs during treatment with ethambutol, the patient should have a complete examination by an ophthalmologist. If a diagnosis of ethambutol toxicity is made, the drug should be stopped at once.

Peripheral neuritis has occurred occasionally among patients treated with ethambutol in large doses. Reports incriminating this drug in other kinds of toxicity have been rare. In our experience involving nearly 700 patients, there have been no hypersensitivity reactions to ethambutol, no gastrointestinal disturbances, and no evidence of toxicity to the liver, kidneys, or hematopoietic system.

Ethambutol can be given for long periods of time and on an outpatient basis. In our total series, 227 patients have received the drug for one year or longer. Two patients (retreatment cases) have received ethambutol for more than 8 years.

The drug is well tolerated by people of all ages. Our series includes 36 patients who were more than 70 years of age and 2 other patients who were 92 and 94 years old when treatment was begun. We have treated three children, two 5 year old boys and a 13 year old girl.

So far, ethambutol has not shown any teratogenic effect in human beings. In our series, four women received ethambutol during pregnancy, two of them treated throughout gestation. All delivered healthy infants and the children have developed normally, the oldest now being five years old.

Initial Treatment of Pulmonary Tuberculosis

In cases of previously untreated tuberculosis, ethambutol has been used successfully in combination with INH or in a three-drug regimen consisting of streptomycin, ethambutol, and INH.

In our own study of these regimens, ethambutol was given in a dose of 20 to 30 mg. per kg. of body weight, a dose of 20 mg. per kg. being used in the great majority of cases; INH was given in a dose of 300 mg. per day; and streptomycin was administered in a dose of 1 gm. daily for 2 to 3 weeks, then 1 gm. twice a week.

Despite the fact that 95 per cent of the total of 113 patients had far advanced disease, sputum conversion occurred within 6 months in all cases (Table 1). At the end of 6 months, sputum cultures were negative for an average period of 3.7 months. Bacterial resistance to the drugs used in the two regimens did not occur in any case. By clinical and roentgenographic criteria, the regimen which included streptomycin was superior to the two-drug regimen.

Since this study was terminated in 1968, a total of 189 additional patients have received streptomycin, ethambutol, and INH as initial treatment, and the results continue to be excellent.

In any regimen which contains INH, and particularly in one which contains both streptomycin and INH, the contribution of an adjunct such as ethambutol or PAS is difficult to assess. In a randomized study by Bobrowitz and Robins, two regimens of treatment with ethambutol and INH were compared with a third regimen consisting of PAS and INH. In the first regimen ethambutol was given in a dose of 25 mg. per kg. for the first 2 months, and 15 mg. per kg. thereafter. In the second regimen ethambutol was prescribed in a dose of 15 mg. per kg. throughout treatment. Sputum conversion occurred within 4 months in 94.6 per cent of the cases in the first regimen, 88.5 per cent in the second regimen, and 82.3 per cent in the third regimen consisting of PAS and INH. Significant improvement radiologically was seen more often in the two regimens which included ethambutol.[2]

In a preliminary report of a cooperative study conducted by the United States Public Health Service, initial treatment with streptomycin, INH, and ethambutol in a dose of 15 mg. per kg. appeared to be less effective than treatment with streptomycin, PAS, and INH in producing sputum conversion.[20] However, adverse reactions were seven times as frequent with PAS as with ethambutol.

The superiority of ethambutol as an adjunct to INH lies in the fact that ethambutol is so well tolerated and accepted by patients. Unfortu-

Table 1. *Initial Treatment Including Ethambutol*

		3 MONTHS		6 MONTHS	
REGIMEN		ETHAMBUTOL + INH	ETHAMBUTOL + INH + STREPTOMYCIN	ETHAMBUTOL + INH	ETHAMBUTOL + INH + STREPTOMYCIN
X-ray improve-ment	Slight	3 (10.4%)	11 (9.6%)	0	3 (3.3%)
	Moderate	14 (48.2%)	44 (38.6%)	6 (25.0%)	10 (11.2%)
	Marked	12 (41.4%)	59 (51.8%)	18 (75.0%)	76 (85.5%)
Number of patients		29	114	24	89
Sputum conversion (by culture)		14 (48.2%)	77 (67.6%)	24 (100.0%)	89 (100.0%)

nately, its cost, although not excessive, is considerably greater than that of most preparations of PAS, and this may be a factor in determining how universally ethambutol is used in initial treatment.

Before prescribing ethambutol in initial treatment, it is important to quiz the patient in regard to previous treatment and even in regard to the source of his infection. If bacterial resistance to streptomycin and INH is a possibility because of primary resistance or previous treatment, ethambutol should be withheld until sensitivity studies are available.

Retreatment of Pulmonary Tuberculosis

The efficacy of ethambutol was originally proved by pilot studies in which the drug was administered alone to patients having drug-resistant pulmonary tuberculosis.[12, 15] In our own study, bacteriologic conversion occurred within 3 months in more than half of a small series of cases, but lasting chemotherapeutic control of the patient's disease occurred in relatively few cases. Bacterial resistance to ethambutol was demonstrated, usually between the third and fifth months of treatment, in 37.5 per cent of the cases in which it was administered alone or in combination with one or two other agents that had been used previously and to which the patients' organisms were resistant in vitro. Bacteriologic relapse coincided with the emergence of organisms resistant to ethambutol in a concentration of 5 micrograms per ml. of medium.

In order to obtain definitive results with any regularity, ethambutol must be combined with other antimycobacterial agents of proved efficacy to which the patient's organisms are susceptible in vitro.

In an attempt to determine the comparative efficacy of combinations of drugs including ethambutol, we have studied the regimens listed in Table 2. In each regimen the patients received only agents which had not been administered previously. All previous chemotherapy, including INH, was discontinued when the new regimen was begun.

Results were excellent when ethambutol was combined with cycloserine in the dosage which we have used for more than 10 years—a total daily dose sufficient to produce a "trough" serum concentration

Table 2. *Retreatment and Sputum Conversion*

	3 MONTHS		6 MONTHS	
REGIMEN	NO. OF PATIENTS	NO. WITH NEGATIVE CULTURES	NO. OF PATIENTS	NO. WITH NEGATIVE CULTURES
Ethambutol alone	16	9 (56.3%)	11	5 (45.5%)
Ethambutol and cycloserine	60	49 (81.6%)	48	43 (89.6%)
Ethambutol, cycloserine, and viomycin	38	31 (81.6%)	28	26 (92.8%)
Ethambutol, cycloserine, and streptomycin	3	3 (100.0%)	1	1 (100.0%)
Ethambutol and ethionamide	21	15 (71.4%)	15	10 (66.6%)

of approximately 30 micrograms per ml. Most patients received cycloserine in a dose of 20 to 30 mg. per kg. of body weight, the total amount being divided into three doses per day. All patients received pyridoxine in a dose of 100 mg. three times daily.

It is true that not all patients tolerate cycloserine. In 5 to 10 per cent of the cases in which it is prescribed, cycloserine has to be discontinued because of psychic toxicity. But in the great majority of cases the combination of ethambutol and cycloserine has been tolerated well and has been given without interruption for periods up to 5 years, in many cases on an outpatient basis.

The addition of viomycin to the regimen of ethambutol and cycloserine did not improve the results significantly, but in three of three cases in which streptomycin had not been administered previously, the regimen of streptomycin, ethambutol, and cycloserine brought about sputum conversion within 3 months.

In our series of 21 cases, the results of treatment with ethambutol and ethionamide in a dose of 750 to 1000 mg. per day were less impressive than the regimens including cycloserine (Table 2).

Other regimens of retreatment including ethambutol have received extensive investigation. In many of these studies ethambutol and one or more other agents have been added to the patients' previously ineffective regimen and, in practically all studies, the administration of INH has been continued, regardless of the degree of INH resistance. This has made it difficult to assess the contribution of ethambutol.

It can be stated that in all regimens of retreatment including ethambutol, sputum conversion has occurred in a sizable proportion of cases. Bobrowitz reported sputum conversion within 4 months in 75 per cent of 28 cases in which ethambutol and INH were combined with either pyrazinamide, cycloserine, or viomycin.[1] In a cooperative study by the United States Public Health Service, ethambutol and INH were combined with a third agent not previously used, and at 16 weeks the percentage of sputum conversion was 82.1 per cent for 28 patients receiving cycloserine (750 mg. per day), 80.6 per cent for 36 patients receiving ethionamide, and 79.5 per cent for 39 patients receiving capreomycin.[23]

A most promising regimen of retreatment consists of ethambutol and rifampin, an agent not yet available commercially, which has been reported to have marked antituberculosis activity in vitro and in vivo. In a series of 12 retreatment cases in which ethambutol and rifampin were added to regimens previously ineffective, sputum conversion occurred within 12 weeks in 11 cases, with subsequent bacteriologic relapse in only one case.[1] In a pilot study of retreatment with ethambutol and rifampin conducted by the Veterans Administration, sputum cultures were negative at 12 weeks in 84 per cent of 20 cases and at 20 weeks in 94 per cent of 18 cases.[17]

Extrapulmonary Tuberculosis

Ethambutol can be used to good advantage in all forms of extrapulmonary tuberculosis in regimens of initial treatment and retreat-

ment. In our experience the regimen of ethambutol and cycloserine has provided definitive therapy in one case of old genitourinary tuberculosis and in one case of disseminated tuberculosis caused by drug-resistant organisms.[16] In this case the patient, a 5 year old boy, received both ethambutol and cycloserine for 3 years and ethambutol alone for an additional 2 years. Another patient having tuberculous meningitis in addition to pulmonary disease of long duration recovered on a regimen consisting of streptomycin, cycloserine, ethionamide, and ethambutol (the only agent not administered previously).[13]

Nontuberculous Mycobacterial Infections

The difficulties of treating patients infected by Mycobacteria other than M. tuberculosis have received much emphasis. In respect to M. kansasii the difficulties may have been exaggerated. During the last 7 or 8 years most strains of M. kansasii studied in our laboratory have grown out as smooth colonies and are susceptible predominantly to streptomycin and INH. Patients infected with such strains respond well to treatment with these two drugs, particularly if the regimen is fortified by a third drug to which the organisms are susceptible in vitro. In our experience, 76 per cent of all strains are completely susceptible to ethambutol, and 28 per cent to PAS.

In the experience of Pfuetze, patients having pulmonary disease caused by M. kansasii have responded well to treatment with streptomycin, INH, and ethambutol in a dose of 20 mg. per kg. of body weight. Twenty-five (70 per cent) of 36 patients had negative sputum cultures within 3 months; 27 (93 per cent) of 29 patients, within 6 months.[11]

In our series, the same regimen brought about sputum conversion within 3 months in 13 of 13 cases, but in one case bacteriologic relapse occurred, owing to the fact that the patient's strain of M. kansasii proved to be highly resistant to INH before exposure to the drug. Herein lies the risk of using ethambutol in initial treatment. In the comparatively rare instances of significant bacterial resistance to streptomycin and INH, the regimen of ethambutol, streptomycin, and INH could, in effect, be monotherapy.

Disease caused by M. kansasii can be treated successfully by ethambutol in combination with other antimycobacterial agents. Ninety-two per cent of the strains tested in our laboratory were highly susceptible to cycloserine; 75 per cent, to ethionamide. In a study including retreatment cases as well as patients treated for the first time, excellent results were obtained by using ethambutol in combination with cycloserine (administered as described above): sputum conversion occurred within 3 months in 17 (81 per cent) of 21 cases and within 6 months in 13 (93 per cent) of 14 cases. Sputum conversion also occurred within 3 months in 2 cases in which ethambutol was combined with ethionamide and in one case in which ethambutol was combined with both cycloserine and ethionamide.

The usefulness of ethambutol in the treatment of disease caused by the Battey type of Mycobacteria (Runyon's Group III) is not so clear. In a group of 14 patients treated for 6 months, Lester et al. reported

sputum conversion in 9 cases (64 per cent) by administering four to six antimycobacterial agents simultaneously, including ethambutol.[9]

Summary

Ethambutol is an antimycobacterial agent of impressive efficacy and low toxicity. It is well tolerated and accepted by patients because it is not a bulky medication, is taken only once a day, and has no unpleasant side effects. The one disadvantage of ethambutol is the relatively small range between the therapeutic and potentially toxic doses. In larger doses ethambutol may cause a reversible type of retrobulbar neuritis. In the dosage now recommended, 15 to 25 mg. per kg. of body weight, the risk of ocular toxicity is negligible. Ethambutol has proved to be a major therapeutic agent in the initial treatment and retreatment of all forms of tuberculosis and in disease caused by M. kansasii; it may also be useful in other nontuberculous mycobacterial infections. Ethambutol should always be prescribed in combination with other agents of proved efficacy, preferably those not administered previously, to which the patient's organisms are susceptible in vitro.

VIOMYCIN

Viomycin is a tuberculostatic agent which has been in use since 1950. It is effective against streptomycin-resistant organisms, but does exhibit some cross resistance with kanamycin and capreomycin, other antibiotics derived from Streptomyces. In vitro and in vivo, viomycin proved to have significant antituberculosis activity, about one-fourth to one-half that of streptomycin.[5, 21]

In human tuberculosis the usefulness of viomycin is limited by its toxicity when administered in therapeutic doses on a daily basis for any length of time. Nephrotoxicity, with associated electrolyte imbalance, was noted frequently in early clinical studies.[21] Damage to the eighth cranial nerve with deafness and, less often, loss of vestibular function also occurred.

The potential toxicity of viomycin can be avoided by limiting the total daily dose to 1 to 2 gm. (administered by intramuscular injection in either one or two doses) and restricting daily administration to 2 to 3 weeks. With intermittent treatment—1 to 2 gm. two or three times a week—viomycin can be given safely for an indefinite period and on an outpatient basis. In our experience, hypersensitivity reactions to viomycin or any other side effects are infrequent.

By present standards, the therapeutic efficacy of viomycin is not great. In an early study in which 23 patients received viomycin alone in the huge dose of 50 to 60 mg. per kg. per day for 30 to 126 days, sputum conversion by culture occurred in only 4 cases.[18]

Viomycin has no place in the initial treatment of tuberculosis. The antibiotic may enhance the chemotherapeutic effect of regimens of retreatment, but this would be difficult to prove. Viomycin is compatible with all the antituberculosis agents which are administered orally, and

has been included in regimens consisting of four or even five other agents. Because of their potential nephrotoxicity, viomycin and kanamycin should never be used together. However we have used viomycin in regimens including streptomycin, each antibiotic being given in a dose of 1 gm. twice a week but being administered on different days. In cases of partial bacterial resistance to streptomycin, we have given both antibiotics in a dose of 1 gm. per day for a period of 2 weeks following pulmonary resection.

Despite its low order of activity, viomycin provides sufficient chemotherapeutic protection to allow resectional surgery to be carried out successfully.[14] When pulmonary resection is indicated in retreatment cases, it is well to reserve viomycin for this purpose, beginning treatment only a few days before surgery to insure a fresh chemotherapeutic effect.

Treatment with viomycin alone results in the emergence of viomycin-resistant strains of tubercle bacilli, and the antibiotic should never be added singly to a regimen which has proved to be ineffectual. In regimens of retreatment, viomycin should be combined with two or more of the best agents available, preferably those which the patient has not received previously and to which his organisms are susceptible in vitro.

This principle applies, also, to the treatment (or retreatment) of patients having nontuberculous mycobacterial disease. In our laboratory, 87 per cent of 40 strains of M. kansasii were inhibited by viomycin in a concentration of 2 micrograms per ml. of medium. Some strains belonging to Runyon's Group III are also susceptible to this antimycobacterial agent.

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Nystatin

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Nystatin is an antifungal antibiotic produced by a strain of Streptomyces noursei. It is, like amphotericin B, a polyene compound with an empirical formula of $C_{46}H_{77}NO_{19}$ and contains four triple unsaturated bonds. Nystatin is fungistatic in vitro against Candida albicans and certain other yeast-like fungi. As far as is known, Candida organisms have not become resistant to nystatin in vivo. It has no demonstrable bacteriostatic activity and its mode of action is unknown.

Nystatin is poorly absorbed from the gastrointestinal tract, skin, or mucous membranes, and is virtually nontoxic and nonsensitizing. No detectable blood levels are obtained when the antibiotic is given in the recommended therapeutic doses. Nystatin is very slightly soluble in water and it loses considerable microbiologic activity in suspension or solution. Even in a dry state, it may lose about 25 per cent of its microbiologic activity in 6 months.

PREPARATIONS AVAILABLE

Tables 1 and 2 list the various preparations of nystatin alone or in combination with other topical agents and also the different vehicles in which these preparations currently are available. Since suspensions and solutions have a limited shelf life, they should be used within the time designated by the manufacturer. The oral suspension is prepared at the time of use and will remain suitable for use for 10 to 14 days, if refrigerated. Very recently, lotions of nystatin alone and in combination with other topical agents have become available. These preparations are reported to be stable and to maintain long term microbiologic activity.

Other than the different vehicles used to incorporate the nystatin, the topical preparations of nystatin may be divided into 4 categories,

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Table 1. *Topical Agents*

CATEGORY	TRADE NAME	CONCENTRATION OF NYSTATIN	VEHICLE	INGREDIENTS	HOW SUPPLIED
I	Mycostatin Powder	100,000 units/gm.	Talc	None	15 gm. squeeze bottle
	Nysta-Dome Lotion	100,000 units/gm.	Water	None	1 oz. bottle
	Mycostatin Cream	100,000 units/gm.	Vanishing cream	None	15 gm. tube
	Mycostatin Ointment	100,000 units gm.	Hydrocarbon gel (Plastibase)	None	15, 30 gm. tubes
II	Nysta-Cort Lotion	100,000 units, gm.	Water	Hydrocortisone ½%	1 oz. bottle
III	Mycolog Cream	100,000 units/gm.	Vanishing cream	Neomycin sulfate; gramicidin; triamcinolone acetonide 0.1%	5, 15, 30 gm. tube; 4 oz. jar
	Mycolog Ointment	100,000 units/gm.	Hydrocarbon gel (Plastibase)	Neomycin sulfate; gramicidin; triamcinolone acetonide 0.1%	5, 15, 30 gm. tube; 4 oz. jar
	Neo-Nysta-Cort Ointment	100,000 units/gm.	Petrolatum	Neomycin sulfate; hydrocortisone 1%	15 gm. tube
IV	Nystaform-HC Lotion	100,000 units/gm.	Water	Iodochlorhydroxyquin 3%; hydrocortisone ½%	1 oz. bottle
	Nystaform Ointment	100,000 units/gm.	Petrolatum	Iodochlorhydroxyquin 3%	15 gm. tube
	Nystaform-HC Ointment	100,000 units/gm.	Petrolatum	Iodochlorhydroxyquin 3%; hydrocortisone 1%	15 gm. tube

Table 2. *Oral and Vaginal Agents*

	TRADE NAME	CONCENTRATION OF NYSTATIN	OTHER ACTIVE INGREDIENTS	HOW SUPPLIED
Oral tablets	Mycostatin	500,000 units tablet	none	Bottles of 12 and 100
Oral suspension	Mycostatin	Reconstituted to 100,000 units/ml.	none	To make 24 ml.
Vaginal tablets	Mycostatin	100,000 units tablet	none	Boxes of 15 or 30
Nystatin-Antibacterial antibiotic capsules	Achrostatin-V	250,000 units caps	Tetracycline HCl 250 mg.	Bottles of 16 and 100
	Declostatin	250,000 units caps	Demethylchlor-tetracycline 150 mg. and 300 mg.	Bottles of 16 and 100
	Terrastatin	250,000 units caps	Oxytetracycline 250 mg.	Bottle of 60
	Tetrastatin	250,000 units caps	Tetracycline 250 mg.	Bottle of 100
	Tetrex-F	250,000 units/caps	Tetracycline phosphate 250 mg.	Bottles of 16 and 100
Nystatin-Antibacterial antibiotic oral suspensions	Achromycin-V	Reconstituted to 125,000 units/5 ml.	Tetracycline HCl 125 mg./5 ml.	To make 60 ml.
	Declostatin	125,000 units/5 ml.	Demethylchlor-tetracycline 75 mg./5 ml.	To make 60 ml.
	Terrastatin	125,000 units/5 ml.	Oxytetracycline 125 mg./5 ml.	To make 60 ml.
	Tetrastatin	125,000 units/5 ml.	Tetracycline HCl 125 mg./5 ml.	To make 60 ml.
	Tetrex-F	125,000 units/5 ml.	Tetracycline phosphate 125 mg./5 ml.	To make 60 ml.

those containing (I) nystatin alone, (II) nystatin with a corticosteroid (hydrocortisone), (III) nystatin with a corticosteroid (hydrocortisone or triamcinolone acetonide) and an antibiotic (neomycin, gramicidin), (IV) iodochlorhydroxyquinoline (present in I or II above)

The selection of a topical anticandidal agent from the table should be based on the following:

1. When nystatin alone is desired for its anticandidal effect, select from Category I.

2. When in addition to the anticandidal effect, an anti-inflammatory and antipruritic action is desired, select from Category II.

3. When in addition to the above, an antibacterial effect is desired, select from Category III. In general, triamcinolone acetonide 0.1 per cent is more anti-inflammatory than hydrocortisone 1 per cent.

4. Iodochlorhydroxyquinoline, in itself, is a moderately effective anticandidal agent. Select Category IV when its effect, in addition to nystatin, is desired.

PRINCIPLES OF THERAPY

The selection of an appropriate vehicle is often important, because it may alter the therapeutic effectiveness of the active ingredient. The following general points may aid in selecting the vehicle.

1. Powders are used in the treatment of intertriginous areas, i.e., between the toes, in the intergluteal cleft, axillae, groin, and infra-mammary areas. They initially exert a drying effect, reduce friction, and frequently provide comfort where mild maceration may be a problem. Powders, however, have a tendency to "ball up" and may prove irritating.

2. Nystatin "lotions" are suspensions which have water as their base. They are convenient to apply and may be used in treating acute inflammatory and exudative candidiasis. In addition to being cooling, lotions also may prove drying. Sometimes, however, lotions are too drying and, if they become crumbly and gritty in the intertriginous areas, irritation may ensue.

3. Creams have the advantage of reduced "messiness" and ease of application and therefore are the most frequently used of all the nystatin preparations. On occasions, use of creams in intertriginous areas may prove irritating, especially in a warm and humid environment.

4. Ointments are generally very well tolerated except for their macerating effect, and onset of possible secondary infection, in the intertriginous spaces, especially when there is excessive rubbing of the adjacent parts. For these reasons, nystatin ointment preparations are best used at night, during the less active hours, and where lubrication might be desired, for example, to relieve excessive dryness, for a soothing effect, as in the perianal region, and in the often constantly wet diaper area.

It is important to remember that patients may develop allergic contact dermatitis to any of the ingredients in these combinations, and continued application to the allergic patients will prolong the illness.

For example, Mycolog cream is a very efficacious nystatin-corticosteroid-antibacterial combination and contains, in addition to gramicidin, the following possible allergic sensitizers — thiomersol, ethylenediamine hydrochloride, and parabens (all preservatives), and neomycin sulfate.

Combined nystatin-tetracycline capsules or oral suspensions should not be prescribed when tetracycline is indicated and there is no clinical evidence of candidiasis. Combined therapy should be used when the patient is debilitated, or has recurrent candidal vaginitis or candidal infection of the anogenital area when taking tetracycline. Occasionally it is necessary to administer more nystatin orally than is available in the combined preparations.

CANDIDIASIS: GENERAL CONSIDERATIONS

Since nystatin is used almost exclusively for the treatment of candidal infections, a brief discussion of candidal disease and its pathogenesis is included.

Candida albicans is a ubiquitous yeast which generally is considered to be saprophytic but may become pathogenic under certain circumstances. The factors which may be responsible for this conversion are the number of organisms present, the environmental milieu, the available nutrients, and the host's immunologic defenses. C. albicans is the most commonly encountered species of candida to produce disease. Candidiasis usually remains confined to the skin and mucous membranes, although it may uncommonly cause life-threatening visceral lesions in particularly susceptible patients. Maceration and heat provide fertile areas in which candida organisms may grow. The intertriginous and mucocutaneous areas of the skin are the most susceptible sites for such infections.

With the increased use of systemic antibacterial antibiotics, corticosteroids and antimetabolites, candidiasis has become an increasing clinical problem. Antibacterial antibiotics may suppress antibiotic-sensitive bacteria and thus allow overgrowth of candidal organisms in the gastrointestinal tract. Corticosteroids and antimetabolites may directly suppress the host defense mechanism, such as antibody synthesis or phagocytosis, and thus allow the individual to become more susceptible to candidiasis. Patients who are pregnant, obese, or debilitated, or have blood dyscrasias, diabetes mellitus, or other endocrinopathies, are more prone to candidal infections. In fact, when the diagnosis of candidiasis is made, other pathologic conditions, especially diabetes, should be sought. Candidal infections may be difficult to cure unless such basic pathologic situations are corrected or controlled.

CLINICAL INDICATIONS FOR THE USE OF NYSTATIN

Candidiasis causes a variety of lesions of the skin, mucous membranes, and viscera. Mechanical factors are frequently responsible for the lowered resistance of the tissues to candidal growth in localized

areas. These areas are nearly always intertriginous, where moisture, warmth, and subsequent maceration of the skin allow the yeast to thrive. Often the management of these factors is more of a problem than the treatment of the infection itself.

Ordinarily, the diagnosis of candidiasis can be made on clinical grounds alone. However, the presence of gram-positive budding yeast on microscopic examination and the rapid growth of the organism on Sabouraud's medium are helpful laboratory aids in diagnosis.

Candidiasis of the Intertriginous Areas

Candidiasis may involve any part of the skin, but, as already noted, it most commonly invades the intertriginous areas where there is poor evaporation of sweat, increased local heat, rubbing, and, finally, maceration. The areas most often involved are the axillae, the submammary region, the genitocrural and intergluteal areas, between the toes, and in the fingerwebs, especially between the middle and ring fingers. Candidiasis may complicate a diaper rash in infants and often is the major component of the dermatitis.

An important part of the management of cutaneous candidiasis is the elimination of excessive maceration. Sweating should be kept at a minimum, moist and wet clothing should be changed frequently, and clothes should be loose and not binding or rubbing. It is important to change an infant's diapers frequently in order to avoid maceration caused by urine. Clean, dry, soft material, such as a double fold of sheeting or similar absorbing material should be placed between skin folds, as under the breasts, between the buttocks, between the toes, and so forth.

A powder or lotion from Category I applied three to four times daily is often helpful in the management of intertriginous candidiasis; in addition to being an anticandidal agent, the powder or lotion is often beneficial in reducing maceration. When annoying inflammation is present, a lotion or cream incorporating a corticosteroid with or without antibacterials may also be used three to four times daily (Category II or III). It is sometimes helpful to use a combination of one of the cream vehicles three times daily and an ointment vehicle at bedtime. It should be remembered that because creams and ointments in intertriginous areas are sometimes irritating and macerating, their use must be carefully supervised. Treatment should be continued for at least 7 to 10 days, even if the eruption clears in less time. In recalcitrant or recurrent cases, especially when there is anogenital involvement, it is often beneficial to give nystatin oral suspension or tablets, 500,000 units four times daily. Should vaginal discharge and itching be associated with anogenital candidiasis, then nystatin vaginal tablets should be inserted daily for at least 2 weeks, in addition to use of topical and oral nystatin.

Nystatin preparations are not always the answer to every candidal infection; at times one must resort to some of the older topical remedies (Category IV).

Perlèche

Inflammation with erosions and fissures at the corners of the mouth is often referred to as perlèche and Candida albicans are frequently

associated. In addition to the macerating action of collections of saliva at the angles of the mouth, another contributing factor is the occlusive effect of a sagging and overhanging upper lip caused by poorly fitting dentures or the edentulous state. Perlèche is commonly seen in children who drool and suck their thumbs. This condition is rarely caused by vitamin deficiency.

Treatment of perlèche depends on its cause. If due to C. albicans, local application of an ointment containing nystatin (Category I or III) four or more times daily is often beneficial. Perlèche is not usually associated with oral candidiasis, but if such is the case, nystatin oral suspension, one teaspoonful four times daily should be given (see below). Treatment should be continued until all signs of inflammation are gone. In chronic cases efforts should be made to correct any faulty dental bite. Unfortunately, perlèche frequently recurs.

Oral Candidiasis

Oral candidiasis (thrush) is a common manifestation of Candida infection and is observed in two distinct age groups. Newborn infants develop the infection in the first few days of life or later in the neonatal period. Presumably they are infected when passing through the mother's vaginal canal. Thrush in older children and adults occurs predominantly in debilitated patients.

Nystatin is effective in the treatment of oral candidiasis. Adequate dosage and frequent administration of the nystatin is important. Four hundred thousand units of the oral suspension (4 ml.) should be given four to six times daily. It is important that the liquid be lavaged over the mucous membranes for about one minute, after which it may be swallowed. Treatment should be continued for 7 to 14 days.

Candidal Esophagitis

Candidal esophagitis is uncommon but may be associated with thrush in infants or with debilitating disease in adults. Since it may be life-threatening, prompt recognition and treatment is important. Nystatin suspension, 400,000 units swallowed four to six times daily, is the appropriate therapy.

Candidal Enteritis

This condition is uncommon. Since C. albicans can be isolated from the intestinal tract of 3 to 38 per cent of healthy children and adults, its role as an etiologic agent in candidal enteritis is not clear. If the diagnosis is suspected, 500,000 units of nystatin (tablets or oral suspension) should be given every 4 hours. Patients ordinarily improve in less than 2 weeks.

Perianal Candidiasis

In treating pruritus ani due to or aggravated by Candida albicans, it is important to remove any underlying contributing factor whenever possible. If the patient is receiving systemic antibacterial antibiotics they should be temporarily discontinued, if possible. Nystatin tablets, 500,000 units, four to six times daily, are necessary to eradicate the

candidal organisms from the gastrointestinal tract and thus stop the seeding and continuous reinfection of the perianal area with the yeast. In addition, topical therapy as outlined for candidiasis of the intertriginous areas must be used diligently.

Candidal Vulvovaginitis

C. albicans is a common inhabitant of the vaginal tract, being found particularly during antibacterial antibiotic therapy, during pregnancy, and in diabetic patients. Although it does not always cause symptoms, it may cause irritation and itching in the entire area. The use of nystatin vaginal tablets twice daily for 2 weeks is usually effective therapy. It is frequently necessary to treat the vulva and adjacent skin with topical remedies, and it is usually convenient and acceptable for the patient to use a nystatin cream (Category III preferred) rubbed in well two to three times daily, and a nystatin ointment (Category III preferred) at bedtime. In recalcitrant or recurrent cases, nystatin tablets, 500,000 units, should be given orally four times a day.

Candidal Balanoposthitis

This infection is seen less frequently than candidal vaginitis, although it is often manifest when the sexual partner has the vaginal infection. Treatment with a Category III cream or ointment six times daily is usually curative. In recurrent (ping-pong) or recalcitrant cases the sexual partner should also be treated (see Candidal Vulvovaginitis).

Paronychia and Onycholysis

Acute and chronic paronychia are generally considered to be candidal infections of the periungual tissues, but occasionally the lesions are due to a mixed infection or to bacteria alone. Persons who frequently have their hands in water, for example, cooks and dishwashers, are most affected. It is therefore logical to advise such patients to avoid overexposure of the hands to water and to wear thin cotton gloves under heavier rubber gloves, whenever possible, for protection.

Acute paronychia can usually be managed by the oral administration of broad spectrum antibiotics and the topical application of preparations from Category III or IV. On rare occasions, incision and drainage may be required. Chronic paronychia may be treated by the application of prescriptions from any of the categories, although III and IV will probably be most helpful. Also, if onycholysis is present, the nail should be cut back to the point of separation from the nail bed approximately every 2 weeks; if not, it is difficult, if not impossible, to get the medications to the sites of involvement. Progress of this condition is slow, and it usually takes 4 to 6 months or longer to achieve a cure. Because of the ease of reinfection of the nail bed, women with candidal vaginitis should be treated appropriately.

Candidal Granuloma, Candidal Endocarditis, Pulmonary Candidiasis, Urinary Tract Candidiasis, and Disseminated Candidiasis

These conditions are very uncommon and are due to invasion of the organism into the tissues. Nystatin is not used as the primary treat-

ment since it is not appreciably absorbed from the gastrointestinal tract. Occasionally the aerosol administration of nystatin may be efficacious in pulmonary candidiasis. Oral nystatin should be used as adjunctive therapy to prevent colonization of the gastrointestinal tract with C. albicans.

SIDE EFFECTS OF NYSTATIN

Extensive clinical use of oral and topical nystatin has shown that it is nontoxic when given in the recommended dosage and that there are virtually no side effects. There are no reported instances of allergic sensitivity. On the other hand, nystatin is not used intravenously or intramuscularly because it is toxic when administered by these routes.

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Griseofulvin

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After more than 10 years, it is well to pause and reflect about the current status of griseofulvin. Griseofulvin is now used less often and with more understanding and laboratory control. Some features of current studies are the efficacy of the new microcrystalline form, continued interest in the mechanisms of action, some concern of toxicity, and techniques of use. The preparation has been changed in an attempt to increase absorption through the development of microcrystals. In simulated intestinal fluid, consisting of phosphate buffer and viokase, a pancreatic enzyme, in water, Katchen and Synchowicz[15] showed that the increased plasma level of griseofulvin was due to the increased dissolution rate. The microcrystalline form is now available in most commercial preparations and is preferred for clinical use. As yet, there is no evidence of increased toxic reactions through increased use of the microcrystalline form.

STUDIES ON FUNGI AND RESISTANCE

The antifungal spectrum of sensitivity to griseofulvin still holds. Sensitive organisms include the superficially invasive dermatophytes. After 10 years, is there evidence of increasing organism resistance to griseofulvin? In studies with Trichophyton rubrum, Trichophyton gypseum asteroides, Trichophyton mentagrophytes, Microsporum gypseum, and Epidermophyton floccosum, Fischer[8] found no evidence of any structural change in these dermatophytes with concentrations of the drug below the effective threshold. These experiments were carried out for more than a year. It is not known, as yet, whether there has been any change in the antigenic properties of the fungi with these concentrations.

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Experiments by Vidmar and his associates[23] indicate that T. Quinck-eanum can not only be made resistant to griseofulvin in vitro and in vivo but can also be made to be nonpathogenic to the guinea pig. Similar experiments were done with T. rubrum and E. floccosum. Robertson, Rosenthal, and Wise[2] have also recorded sporadic resistance to griseofulvin in in vivo and in vitro experiments. Alteras and Evolceanu[2] have investigated the different responses of fungi to griseofulvin in Romania as compared to those in other countries. They indicated that some of the strains were more resistant than similar strains from India, for example. They indicated also that the usual nonpathogenic soil keratinophilic fungi were more resistant to griseofulvin than the common dermatophytes: "While an average of 5 micrograms per ml. or even less concentration of griseofulvin is sometimes required for the total inhibition of the growth of various pathogenic dermatophytes, the keratinophilic fungi need a double concentration, at least, for their minimum inhibition in vitro."[2]

In experiments with sensitivity of T. rubrum after our patients had relapse while still under griseofulvin therapy, Schwarz[18] did not find increased resistance to griseofulvin. The dynamics of these recurrences under therapy are not understood.

Blank and Rebell[3] have devised griseofulvin-containing media to help the general practitioner to differentiate between pathogenic superficial dermatophytes which will respond to griseofulvin, and dermatophytes and yeasts which do not. One tube used in their study had chloramphenicol cycloheximide glucose agar and the other had griseofulvin as well. The dermatophytes did not grow on the griseofulvin media but did on the other. Nonpathogenic saprophytes grew well on both. Schwarz[18] agrees it is good discipline for the general practitioner to do fungous cultures, but not for the laboratory. The extent of the actual use of this excellent tube combination is not known at present.

As additional evidence of the presence and persistence of griseofulvin in the skin and hair shaft (also the nails) we have the study of
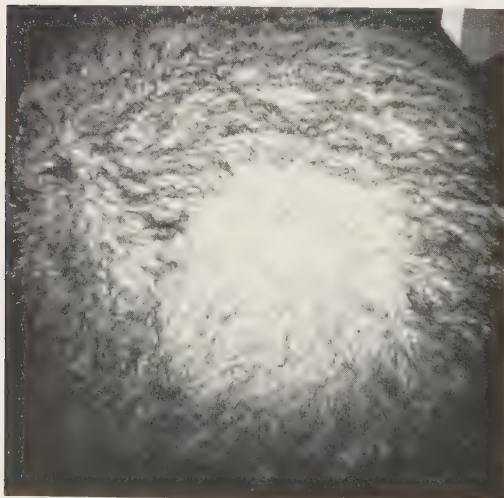
Figure 1. Tinea capitis from nonfluorescent Trichophyton tonsurans — not as easily treated by griseofulvin as tinea capitis caused by Microsporum audouini.

Verma.[20] He used hairs from children on long-term griseofulvin therapy for Microsporum audouini. These hairs, unlike normal hairs, resisted "penetration" in their proximal areas by stock cultures of Trichophyton mentagrophytes. In the past, labeled griseofulvin has helped to localize the griseofulvin in keratin and in invasive fungi.

The influence of corticosteroids, griseofulvin, and tolnaftate on Trichophyton rubrum and Trichophyton mentagrophytes have been studied by in vitro experiments by Caplan and Claybaugh.[5] They found that the steroid hormones may either foster or impair the antifungal properties of both griseofulvin and tolnaftate.

RECENT TOXICITY STUDIES

The usual and more common reactions to griseofulvin continue to be headache, nausea, and vomiting. With nausea and vomiting, we try dose regulation and ingestion with meals, if possible; with headaches, we discontinue medication. Other toxicity studies in the past have been concerned with urticaria, angioedema (not related to penicillin sensitivity), occasional blood dyscrasias, and hepatotoxicity. At present, the chief interest concerns the possible antimitotic effect of griseofulvin and hepatotoxicity, with special reference to photodermatitis and the drug's effect on porphyrin metabolism.

Malawista, Sato, and Bensch[17] have studied and compared the effect of vinblastine and griseofulvin on the living mitotic spindle of Petciania oocytes. They found, actually, that griseofulvin was superior to vinblastine and even demecolcine (Colcemid) on the rapid, reversible, and repeated dissolution of the spindle. They called griseofulvin an "arrester in metaphase." There is no clinical evidence that genetic disturbances are produced in the female, and no effect on sperm has been seen. Our studies of the effect on the hair bulb, by local injection in man showed no effect on the hair cycle or pigment production. However, the clinical rule still holds that griseofulvin should not be given to the pregnant woman.

Early studies on hepatotoxicity in animals were done more than 10 years ago by Schwarz and Barich.[19] There is still concern today of liver involvement, and liver profile studies are recommended at intervals in patients on long-term programs.

The chief interest today is in the effect of griseofulvin on porphyrin disturbances. Ziprokowski and his associates[23] found no changes with microcrystalline griseofulvin, 15 mg. per kg. body weight given daily in four doses for 6 days.

Watson and his associates[22] have studied the effect of griseofulvin on porphyrin metabolism. They found no disturbances of porphyrin metabolism in "any marked degree." There was "inconsistence and variable, at times significant, increase in fecal porphyrin." This excellent report is important clinically, according to Harber,[12] since previous studies had suggested that griseofulvin can induce increased synthesis of ALA synthetase. Thus, at present, it is felt that griseofulvin is not a porphyrogenic substance.

Photodermatitis can develop from griseofulvin, and this fact should be considered when photodermatitis develops in a patient on griseofulvin therapy. This should also be considered when the drug is suggested for patients who have had episodes of various types of photodermatitis in the past. Chang[6] reported on a patient with both photosensitivity and cold urticaria.

The concern for the development of cirrhosis, evident or "silent," with programs maintained for a long time, especially for onychomycosis, still holds as well as for the development of blood dyscrasias. Most of the patients requiring dermatological griseofulvin therapy are young and healthy. When griseofulvin is used for bursitis and angina in elderly patients, there should be increasing concern about the possibility of visceral toxicity.

THE THERAPEUTIC PROGRAM

We would agree that after this long 10-year interval of the use and abuse of griseofulvin we have been disappointed. The initial careful reports should have prepared us for the rather limited use of the drug, controlled by critical clinical judgment and laboratory studies. In brief and dogmatic fashion, the rule still holds that the value of griseofulvin diminishes rapidly as one goes from the head down.

The introduction of microcrystalline forms gave us more effective, and initially more expensive, therapeutic effects for those conditions for which griseofulvin is indicated.

The use of microcrystalline griseofulvin still does not permit us to answer the ever present challenge of the continued failure of consistently positive results for griseofulvin applied topically. Other investigators, such as Kaminsky,[11] and Brandt, Borchardt, and Krause,[4] have reported results with topical griseofulvin as we did.[10]

The usual parameters for a topical preparation were considered – the form of griseofulvin, the vehicle, and the addition of adjuvants to promote penetration and absorption. The microcrystalline form, which was not available to us initially, should help in future studies. However, a recent study with this form in a cream vehicle showed no therapeutic value over the control base.

The next concern for topical griseofulvin is a suitable vehicle and, actually, this phase will have to wait the release of DMSO. Our initial studies with this as a vehicle for griseofulvin were, of necessity, incomplete and have not been continued. Brandt, Borchardt, and Krause[1] added 3 per cent salicylic acid to a 5 per cent griseofulvin salve. With suitable controls, they had good results.

So, at present, topical griseofulvin is still investigative and not routine therapy, and investigations in this area should be continued.

For oral administration, the tendency now is to use for the adult 500 mg. of microcrystalline griseofulvin twice a day, after meals; a high-fat meal increases absorption. The average course is 3 to 6 weeks for tinea of the body with Trichophyton rubrum and Trichophyton mentagro-

Figure 2. Relapse of Trichophyton rubrum onychomycosis on continued oral griseofulvin—after initial clearing with previous negative cultures. Cultures now positive and fungus not resistant in vitro to griseofulvin.
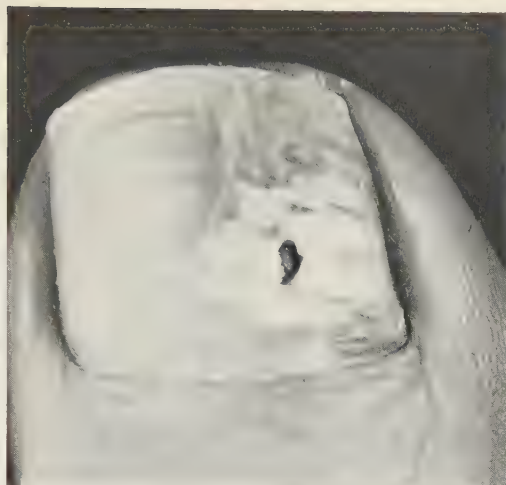
phytes. Akers[1] recommends, from experiences in Vietnam, that treatment should be continued for at least 2 weeks after all is clear to prevent relapse. Prophylactic griseofulvin was used in the Mekong Delta, 0.5 gm. orally, 5 days a week. This reduced the incidence from 35 per cent to 8 per cent; with 1.0 gm. the reduction was to 3.5 per cent.[1]

As indicated previously by the general rule of effect, cephalad down, tinea capitis responds well. Hildick-Smith[13] indicates that a daily oral dose of 250 mg. of griseofulvin is given to children up to 10 years of age, 500 mg. daily in older children. Four to eight weeks are the usual courses. Where daily doses cannot be given, for example, in control of epidemics in rural or tropical areas, single doses of 3 gm. may be given once a week.[9] We would agree that local fungicidal and fungistatic medications should be used with griseofulvin in treating tinea capitis. These may be salicylic creams, ammoniated mercury, or copper creams. To prevent spread of infected hairs, a protective cap should be worn. Griseofulvin is discontinued when fluorescence is negative for those fungus-infected hairs which fluoresce, and when three repeated cultures are negative. Gonzalez-Ochoa, Recoy, and Bravo-Becherille[11] found with experimental inoculation of Trichophyton concentricum on the forearm of 100 boys, griseofulvin, 0.5 gm. daily once a day after the midday meal, had no prophylactic effect but did have a definite therapeutic effect.

In fungal intertrigo and tinea pedis, the results with griseofulvin therapy are often poor and topical agents must be used. Here, certainly, environmental factors play a role in the actual control of the infection, its relapse, and re-infection. For tinea pedis, the wearing of shoes, friction, and sweating make for ease of relapse. Even the continued use of griseofulvin under these circumstances is not effective. It was hoped that effective topical griseofulvin would be the answer here. As yet, it is not.

Kompmann[16] presents the difficulty of griseofulvin therapy for onychomycosis even with concomitant removal of the nail as Demis and
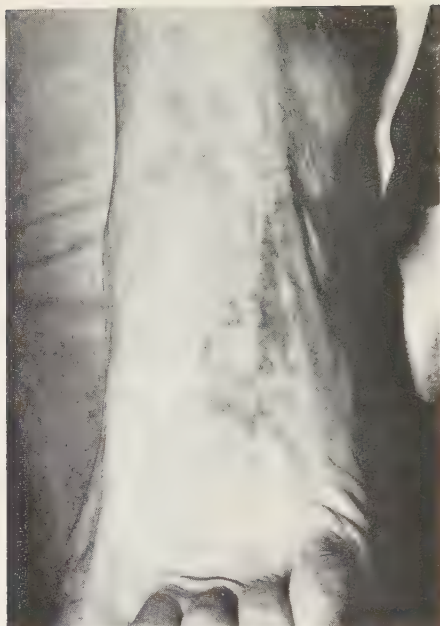
Figure 3. Eczematous dermatitis of the foot simulating tinea pedis – although scrapings and cultures for fungi were negative, griseofulvin had been given without results.

we still recommend. Kompmann[16] reported that the chances of persistent healing were not great, being 40 to 50 per cent. Relapse (or re-infection?) developed. For onychomycosis of the toenails, most patients will not tolerate, therapeutically or economically, the prolonged courses of griseofulvin required.

Unless good control studies are done, it is not always possible to tell the true value of griseofulvin and the combined topical medications such as tolnaftate, salicylic preparations, or copper salts in those patients who require topical agents.

MISCELLANEOUS CONDITIONS. Griseofulvin is used for arthritis and bursitis, although the mechanism of its action is completely unknown. As yet, it has not been proved to be of value in any extensive clinical immunosuppressive therapy program. It is important to note that griseofulvin interferes with the anticoagulant effect of Coumadin (warfarin), and higher doses are required of the anticoagulant.[7]

CONCLUSIONS

After more than 10 years of experience, griseofulvin has maintained its value as an effective antifungal antibiotic for those superficial dermatophytes which are sensitive to it, especially those on the scalp and body. It has been disappointing where it is needed for the all too common tinea pedis and intertriginous infections. Microcrystalline forms are readily absorbed. Fungal resistance can develop. As yet, clinically, this is not significant. Toxicity can develop and usually it is dose related.

Control visceral studies are necessary for long-continued therapy pro-
grams. Griseofulvin is not porphyrogenic, but it is hepatotoxic, and
photodermatitis can develop. For generalized infections with Tricho-
phyton rubrum, continue to look for systemic conditions which make
for abnormal keratin. The challenge of a uniformly effective topical
griseofulvin still remains, as well as the challenge to develop oral anti-
fungal antibiotics more effective than oral griseofulvin.

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Nalidixic Acid in Acute and Chronic Urinary Tract Infections

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Oral Use

A recent review of the use of nalidixic acid (NegGram)[10] has indicated that this drug, given orally, has a wide area of usefulness in the treatment of urinary tract infections. Clinicians have been guarded in the use of the drug in the first trimester of pregnancy, although no teratogenic response has as yet been reported.

The range of side effects, such as photosensitivity, a bullous skin rash, and some disturbance of appetite, at the recommended dose of 4 gm. a day, has now been enlarged to include temporary yellow vision, other cutaneous allergies, diminished hemoglobin, and increased serum glutamic oxaloacetic transaminase. All these latter are seen as periods of administration extend beyond 2 months.

The failure of the early literature[1, 2, 4, 5] to point out that alkalization of the urine markedly increases the urine levels of the drug may have resulted in diminished effectiveness of some of the regimens studied. It has been shown that nalidixic acid is almost unique among antibacterial agents (matched only by kanamycin) in having no adverse effects on phagocytosis in concentrations up to 2500 micrograms per ml. Early suggestions that the bacterial population would rapidly develop resistance have not been borne out in the first few years of our usage, nor by other recent reports (Table 1)[9]. One-step resistance has been reported.[6, 10]

Intravenous Use

The experimental availability of nalidixic acid as the sodium salt in 10 per cent solution led us to investigate the usefulness of this agent in systemic infections arising largely from genitourinary infections. With a dose of 15 mg. per kg. of body weight each 8 hours, blood levels were highly variable, but the mean ranged between 30 and 50 micrograms per ml., a level high enough to control 70 per cent of our most resistant cases of Aerobacter-Klebsiella gram-negative sepsis. It was notably not effective at all in any of the cases of sepsis due to Pseudo-

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Table 1. *Sensitivity of Various Microorganisms to Nalidixic Acid*
(50 micrograms per ml.)

	P. morganii	P. mirabilis	P. vulgaris	Pseudomonas	Staph. albus	E. coli	Klebsiella	Serratia	Mima	Herellea
Seneca (1966)[9]	100%	–	100%	0%	–	30%	63%	–	–	–
Stamey (1968)[10]	100%	100%	–	0%	30%	90%	70%	–	–	–
Findley (1969)[3]	–	42%	–	14%	–	53%	34%	9%	14%	18%

monas. Puzzling was the finding that systemic infections due to E. coli were less than 50 per cent susceptible to these high blood levels achieved by infusion. This may be due to the fact that 93 per cent of nalidixic acid is plasma bound.

In some instances it was felt that the drug had been life-saving, although because of the experimental nature of the drug and limited supplies, many cases were treated with an additional drug either before, during, or after the course of intravenous nalidixic acid. The longest any patient was carried on intravenous nalidixic acid alone was 3 weeks.

Long-Term Oral Therapy with Nalidixic Acid

METHOD OF STUDY.   Nalidixic acid (NegGram) was included in a group of drugs used for long-term medication in an earlier study of pyelonephritis. On the basis of this previous study, in which it was found that much of what was normally observed and followed had little or no prognostic significance,[11] care was taken to include in the present survey only those characteristics which *did* have prognostic significance. Pre-treatment and post-treatment culture response, urinalysis response, and blood changes are reported here, together with the incidence of side effects. It is significant that the use of NegGram for more than 6 months was stopped because of the increasing number of side effects that accumulated as the study progressed.

EVALUATION OF RESULTS.   *Culture response.* In a total of 129 patients treated by us for chronic urinary tract infection who had both pre-treatment and post-treatment cultures, favorable initial responses were obtained in 78 patients. All the patients yielded sufficient data for evaluation of results. A response was considered unfavorable if the patient retained his initial infection or proceeded from a negative to a positive culture for a new organism while he was on therapy.

Urinalysis response. Improvement was defined in urinalysis by diminution in pyuria, red blood cells, or albuminuria. Among patients treated less than 2 months, 12 of 44 patients improved, and of those treated for more than 2 months continuously, 18 of 45 patients improved. Since only 89 patients had had pre-treatment and post-treatment urinalyses, there was insufficient data to make any judgment in the

remaining patients. In general, however, therapy over 2 months at a time would seem desirable.

Symptomatic relief.   Symptomatic clinical response was based on a variety of criteria, depending on the individual patient, since the symptom pattern in the individual patient was found to vary over a considerable range. In general, the response was considered to be excellent if all presenting symptoms disappeared while the patient was on the drug. The response was considered to be good if one or more of the symptoms disappeared, moderate if there was no change, and poor if symptoms intensified or a new symptom appeared.

Data regarding evaluation of symptoms were available on 136 patients. Among 73 of these patients who took the drug for less than 2 months, excellent or good results were seen in 15, and moderate to poor results were seen in 58. Among 63 patients who took the drug for more than 2 months, excellent or good responses were seen in 30, and moderate or poor responses were seen in only 33. Again, this would tend to indicate that short-term therapy, of less than 2 months, does not give as good results as a longer course, if symptom relief is used as a criterion.

Side Effects.   Of the same 136 patients, no side effects were noted in 116, and side effects were seen within the first 2 months in 15; among 5 in the long-term group there was one instance of nausea, one of photophobia, one of stomatitis, and one of urethral irritation. One patient discontinued use of the drug because of vague complaints of drowsiness, aches and pains, and loose bowel movements which may not have been related to use of the drug.

Other Laboratory Changes.   Of the 88 patients of the study group who presented themselves for all blood data determinations, 58 showed no blood changes whatsoever. This group was evenly divided between those receiving short and long courses. Diminished hemoglobin or increased blood urea nitrogen was noted in 23 of the 88. These adverse changes were found in 16 patients taking the drug beyond 2 months and in only 7 on short-term therapy. An increase in serum glutamic oxaloacetic transaminase, which in contrast, occurred in only 7 patients, tended to appear early in the therapeutic course if at all.

Intravenous Therapy with Nalidixic Acid

We feel that by giving nalidixic acid intravenously we can achieve blood and urine levels that are 20 to 50-fold higher than the blood levels necessary to overwhelm any organism studied if that organism is restricted to the urinary passages themselves. There is considerable doubt that nalidixic acid should be used in potentially pregnant women or in children under 1 year of age, because there is evidence that the fetal or neonatal liver may not have adequate enzyme systems to handle this drug.

We have used intravenous nalidixic acid in 25 patients for a total of 28 courses. It was reserved for use in desperate situations when, in many instances, a blood culture had indicated that nalidixic acid was the only drug to which the organism was sensitive, or when the existing therapy had failed to control the situation. There were two deaths in

this series, both of them occurring after nalidixic acid had been discontinued for at least 24 hours. The results in the surviving patients were extremely promising. Of 12 cases in which nalidixic acid was used alone, results were good or excellent in 7.

When intravenous nalidixic acid was used as supplemental therapy in patients already receiving colistin, results were excellent or good in 5 of 7 patients. When used in conjunction with chloramphenicol, results were good or excellent in 3 of 6 patients. No other outstanding combinations appeared among the small number of other patients receiving combinations of antibiotics.

It must be pointed out that Seneca,[9] using more than 25 micrograms of nalidixic acid per ml. as a criterion, found that 40 per cent of all clinical strains in bacteremia were resistant to nalidixic acid, so that firm indications must be present to justify the use of intravenous therapy.

SUMMARY

Our own experience bears out that of others, that nalidixic acid is useful in short-term therapy for urinary tract infections, and can be used intravenously with gram-negative sepsis. Our experience should be considered in the light of that of others, here and abroad, who have been more enthusiastic than ourselves about long-term use of the drug in patients with marginal renal function.[1, 4, 6-8, 10]

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